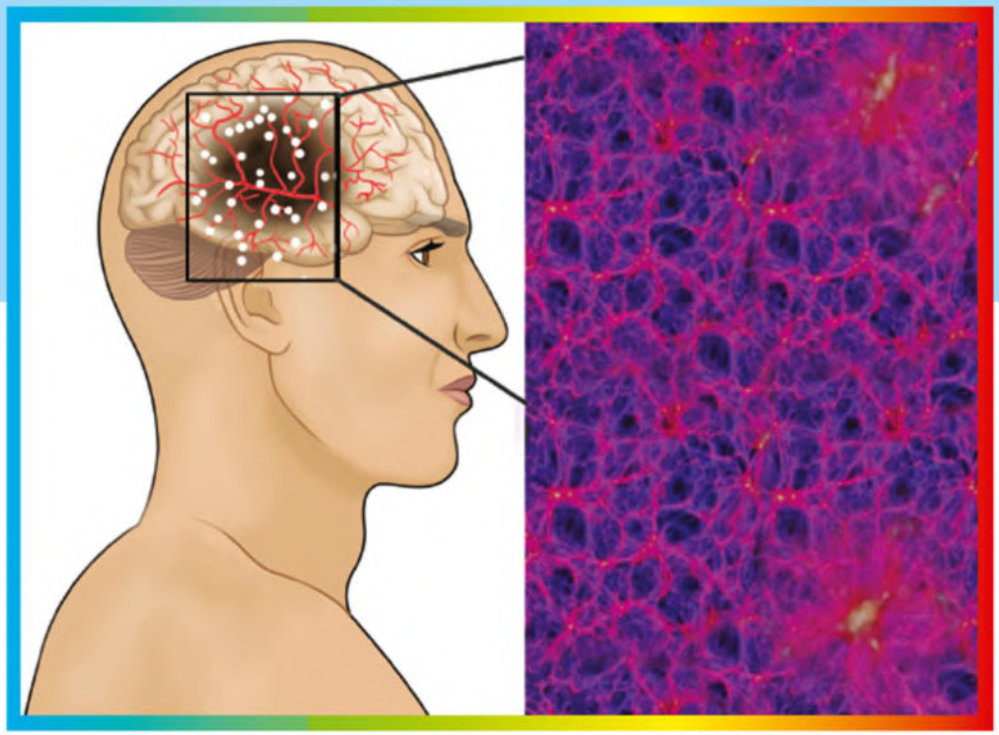
Progress in Clinical Neurosciences

Sumit Sinha
Debashish Chowdhury

Volume 37



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Progress in Clinical Neurosciences

Volume 37

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Contents

Preface vii

Executive Committee of the Neurological Society of India: 2023–24 ix

Contributors xi

General

1. Flow Diversion in Aneurysmal SAH 1
Nitin Narayan Dange, Mayur Gopichand Gharat, and Kushal Bhatia
2. Incidental Gliomas 9
Krishnamurthy Sridhar, Siddarth Kannan, and Ashwin Sridhar

Controversies in Neurosciences—Brain

3. Deep Brain Stimulation in Early Parkinson's Disease Is Useful 15
Hrishikesh Kumar, Debapriya Mukherjee, and Jacky Ganguly
4. Medication-Overuse Headache: Detoxification Is the Key 20
Navendu N. Jana, Arindam Ghosh, Arindam Das, and Pahari Ghosh
5. Awake versus Asleep Mapping for Gliomas 27
Prakash Shetty, Vikas Singh, Parthiban Velayutham, and Aliasgar V. Moiyadi
6. Programmable Shunts for Infantile Hydrocephalus: A Controversial Choice or a Scientific Paradox? 36
Suhas Udayakumaran
7. Molecular Profiling for Brain Tumors—A Necessity or Luxury? 41
Vani Santosh and Shilpa Rao
8. Gamma Knife Radiosurgery for High-Grade Gliomas 52
Shweta Kedia, Sarvesh Goyal, and Deepak Agarwal
9. Mechanical Thrombectomy in Acute Stroke: India Is Still Far Behind 57
Deep Das, Uddalak Chakraborty, and Shashvat Desai
10. Vagal Nerve Stimulation (VNS) versus Deep Brain Stimulation (DBS) for Intractable Epilepsy 62
Aditya Gupta, Pawan Goyal, and Sanjeev Srivastava
11. Tuberculum Sellae Meningioma: Transcranial Microsurgical Excision 73
Sunil Kumar Gupta, Sushant Kumar Sahoo, Apinderpreet Singh, and Sandeep Mohindra
12. Tuberculum Sellae Meningioma: Surgical Nuances of the Endoscopic Endonasal Approach and Recent Concepts 80
Chandrashekhar E. Deopujari, Archana Madhukar Kamble, Vikram Karmarkar, and Nishit Shah
13. Asymptomatic Carotid Stenosis 99
Paritosh Pandey, Saurabh Sinha, Parth Joshi, Ullas V. Acharya, and Pallavi Nyalkalkar
14. Asymptomatic Carotid Stenosis—Is Best Medical Management Enough? 116
Samba Murthy Krishna Mohan Mavuru and P. N. Sylaja

Controversies in Neurosciences—Spine

15. High-Grade Spondylolisthesis—To Fuse in situ or Reduce 125
Savitr Sastri B. V.

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16. Recurrent Lumbar Disk Herniation: Fusion versus Repeat Diskectomy 135
G. R. Vijay Kumar

17. MIS versus Open TLIF—Results and Complications 142
Rushabh M. Chheda, Ashutosh Kumar, Vandan Raiyani, and Jayesh Sardhara

18. Long-Segment versus Short-Segment Fixation in Thoracolumbar Trauma: When to Do It? 153
Deepak Bhangale, Sudhir Dubey and Amrita Endow

19. Controversies About ACM Surgery 163
Kuntal Kanti Das, Nitish Ranjan, Pawan Kumar Verma, Kamlesh Singh Bhaisora, Arun Kumar Srivastava, and Awadhesh Kumar Jaiswal

20. Nerve Transfers in Spinal Cord Injuries 176
Ketan Desai, Alay Khandhar, Pooja Salunkhe, Subhashree Hari, and Anushtup Raval

21. Protons Beam versus Conventional Radiation in Chordomas 188
Srinivas Chilukuri, Ramakrishna Kamath, and Rakesh Jalali

22. Current Treatment Paradigms in Management of Cervical Disk Disease: ACDF versus Disk Replacement, the Controversies! 195
Sachin Anil Borkar, Kushagra Pandey, Akshay Ganeshkumar, P K Sahoo, and Shashank Sharad Kale

23. Role of Anterior versus Posterior Approach for Cervical Spondylotic Myelopathy—A Narrative Review 205
Hemant Bhartiya, Sushil Patkar, Chandan Mohanty, Vivek Vaid, Sankalp Bhartiya, Akshay Mangal and Pradnya Patkar

Case Based Discussions—Defining the SOP's

24. Case of Anterior Third Ventricular Tumor 219
Shashwat Mishra and Hitesh Kumar

25. Trigeminal Neuralgia: Current Understanding and Management Review 226
Amol Mittal and Adesh Shrivastava

General Neurology

26. Treatment of TB Meningitis Should Be for at Least 18 Months 236
Debaleena Mukherjee, Alak Pandit, and Souvik Dubey

27. Ocular Myasthenia Gravis Should Be Treated as Aggressively as Generalized Myasthenia Gravis 251
Jasodhara Chaudhuri and Kartik C. Ghosh

28. Should Thymectomy Be Done in All Patients with Myasthenia Gravis? 259
Vishnu V. Y.

29. Comprehensive Stroke Center—Challenges and Lessons Learned 264
Vijaya Pamidimukkala and Yelamanchi Ramachandra Prasad

30. Surgical Evaluation of Refractory Epilepsy: Can We Make a Cost-Effective Standardized Protocol for India? 272
Swapan Gupta

31. Hearing and Facial Preservation in Acoustic Neuroma—Tips and Technical Nuances 283
Basant K. Misra, Abhijit Warade, and Alay Khandhar

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Preface

The field of clinical neuroscience has undergone remarkable transformations over the past few decades, evolving at an unprecedented pace. As we delve deeper into understanding the complexities of the human nervous system, we unveil new insights that bridge the gap between basic neuroscience research and clinical practice. This 37th volume of "*Progress in Clinical Neurosciences*" is a compiled culmination of efforts by the Neurological Society of India (NSI) in pursuing and imparting knowledge and education to all those who are interested in enhancing their learning in neuroscience. This book aims to capture the progress made in this dynamic field, providing a comprehensive overview of current advancements, emerging therapies, and innovative diagnostic approaches. The theme of this year's CME is "*Controversies and Consensus Opinions*"!

This year's CME encompasses a wide array of topics, ranging from neurodegenerative disorders, neurovascular diseases to neurodevelopmental, spinal disorders, neuro-oncology and traumatic brain injuries. As researchers and clinicians, we are equipped with a better understanding of the underlying mechanisms of these conditions, aided by technological advancements such as neuroimaging, genetic profiling, and biomarker discovery. These innovations not only enhance diagnosis but also pave the way for personalized treatment strategies, enabling us to tailor interventions to individual patient profiles. The star highlight feature of this year's CME will be insightful debates on burning topics in neurosciences by stalwarts in the field and formulating the standard operating protocols for some common diseases in neurosciences.

The contributions within this volume are from leading experts in the field who share their knowledge and experiences, presenting cutting-edge research findings and clinical applications. Each author brings a unique perspective, highlighting the interdisciplinary nature of clinical neuroscience and the collaboration between various domains of science, medicine, and technology.

As we look toward the future, this book serves as a testament to the progress we have made and the challenges that remain. It is our hope that the information presented herein will inspire further research, foster collaboration, and ultimately improve patient outcomes. We invite readers—clinicians, researchers, students, and enthusiasts—to engage with this work, to explore the advancements in clinical neuroscience, and to contribute to the ongoing dialogue that is shaping the future of brain health and medical care.

In closing, we extend our gratitude to all the contributors, as well as the researchers and clinicians who tirelessly strive to push the boundaries of knowledge and improve the lives of those affected by neurological and psychiatric disorders.

Quantum consciousness is a speculative concept that posits a connection between the principles of quantum mechanics and the nature of consciousness. It suggests that quantum phenomena, such as superposition and entanglement, might play a role in cognitive processes and subjective experience. This idea challenges traditional views of consciousness as merely a byproduct of classical neurobiology, proposing instead that consciousness could emerge from quantum states or processes occurring within the brain's microstructures,

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such as microtubules. While still controversial and not widely accepted, quantum consciousness invites intriguing questions about the nature of reality, the mind, and the potential interplay between consciousness and the universe, as depicted in the cover image.

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1 Flow Diversion in Aneurysmal SAH

Nitin Narayan Dange, Mayur Gopichand Gharat, and Kushal Bhatia

History and Introduction

Medical field and medical research have been fueled by technology in recent times. Technological advancements in neuro-intervention have propelled this field from being almost nonexistent about 35 to 40 years back to arguably the most exciting sub-speciality in neurosurgery/neurology in recent years. Complex neuro-vascular pathologies, which required morbid open neurosurgical procedures earlier, can now be attempted and successfully treated using the latest endovascular devices and techniques.

Conventional neurosurgery has its own indications and advantages when it comes to treatment of ruptured intracranial aneurysms (IAs). However, the effectiveness and safety profile demonstrated by various endovascular devices in tackling these tricky "balloons in the brain" have been well established now. Specific morphologies, as shown in **Fig. 1.1**, like wide-neck bifurcation aneurysms, blister aneurysms, side wall aneurysms, fusiform, dissecting aneurysms, etc. have been challenging to treat using traditional endovascular techniques like coiling, assisted coiling, etc..[1] This scenario is now changing with the advent of flow diversion technology and the newer generation devices.

In this chapter, we highlight the important technical features of flow diverters (FDs) and review the essential clinical literature discussing their use in the treatment of complex ruptured IAs.

Flow Diversion Technology and Devices

Intraluminal FDs are "stent-like" devices with low porosity and high pore density. The basic pathological changes for the occurrence of an aneurysm are the weakness of the intima, atherosclerosis, injury, or infection of the arterial wall. We have evolved from the concept of intra-aneurysm filling or parent artery occlusion to repair of the pathological arterial wall.

The concept of FD is based on two principles[2]:

- Placing a woven mesh device in the parent artery changes the blood flow away from the aneurysm sac leading to intrasaccular stasis and thrombosis, as governed by the principles of Virchow's triad.
- The device structure provides a scaffold for the formation of a neointimal endothelial layer across the aneurysm neck.

Initial FD studies have shown that stents with a braided design with minimized porosity and metal coverage of around 30 to 35% produced the maximal intended effect of aneurysm flow diversion and perforator preservation. In short, this combination results in just enough flow diversion to produce intra-aneurysmal stasis and thrombosis without occluding important adjacent vessels supplying normal brain that the stent may cover.[3,4]

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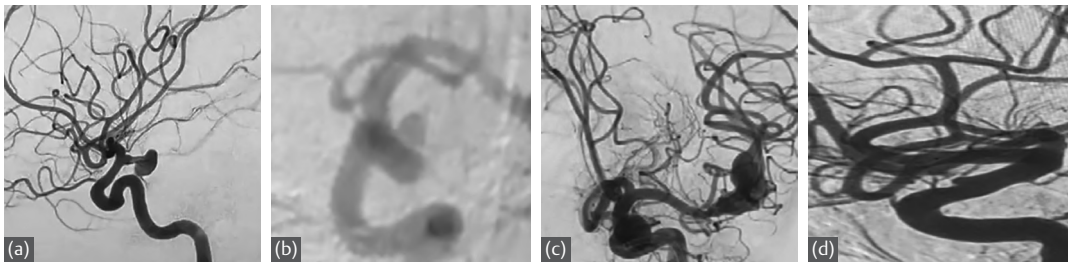

Fig. 1.1 Different types of aneurysm morphologies that may be encountered: **(a)** Dissecting aneurysm arising from the communicating segment of the internal carotid artery. **(b)** Wide-neck saccular aneurysm arising from the ophthalmic segment of the internal carotid artery. **(c)** Fusiform aneurysm arising from the middle cerebral artery. **(d)** Blister aneurysm arising from the dorsal internal carotid artery.

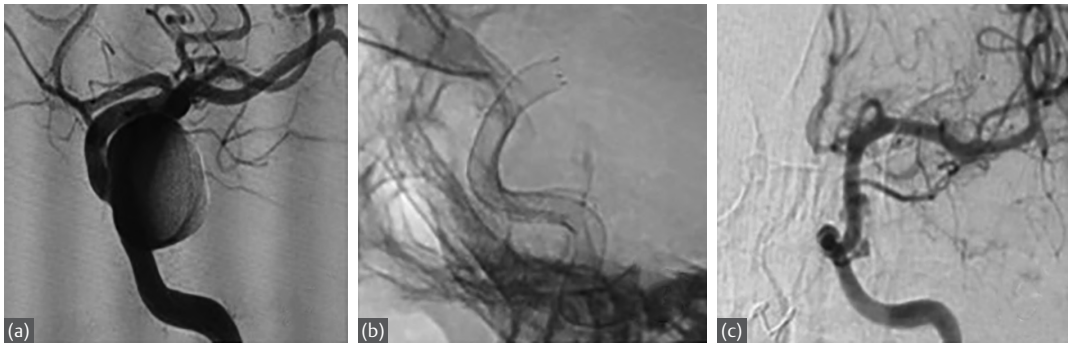

Fig. 1.2 **(a)** Giant, wide-neck, fuso-saccular cavernous aneurysm. **(b)** Endoluminal reconstruction of the dysplastic vessel with a flow diverter. **(c)** Follow-up angiogram showing complete exclusion of aneurysm from circulation.

Some of the commercially available FDs are Pipeline Vantage (Medtronic, USA), Silk Vista (Balt, France), Surpass Evolve (Stryker, USA), Flow Re-direction Endoluminal Device (FRED X) (Microvention, USA), Derivo 2heal (Acandis, Germany), and p64 Flow-Modulation Device (Phoenix, USA).

The mechanisms of action for FDs involve three phases[5,6]:

- The hemodynamic phase.
- The thrombus formation phase.
- The endothelialization phase.

The hemodynamic phase occurs immediately after the procedure, utilizing obstruction of blood flow into the aneurysm from the parent artery related to the resistance created by the mesh component of the FD. Blood flow velocity inside the aneurysm is then markedly reduced, followed by immediate activation of platelets with progressive formation of a stable thrombus over a period of days to weeks, representing the thrombus formation phase. The endothelialization phase involves the transformation of the thrombus to the final collagen stage over a period of several months to years. The transformation of intra-aneurysmal thrombus to collagen leads to a final reduction in the aneurysmal mass.

Some illustrative cases showing this mechanism are shown in **Figs. 1.2–1.5**.

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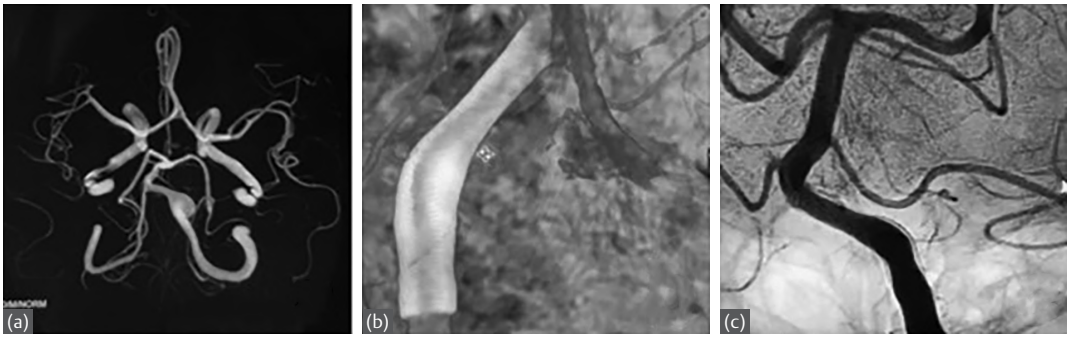

Fig. 1.3 **(a)** Ruptured dissecting aneurysm of left vertebral artery. **(b)** Endoluminal reconstruction of the dysplastic vessel with a flow diverter. **(c)** Follow-up angiogram showing endothelialization of the flow diverter with complete exclusion of aneurysm from circulation.

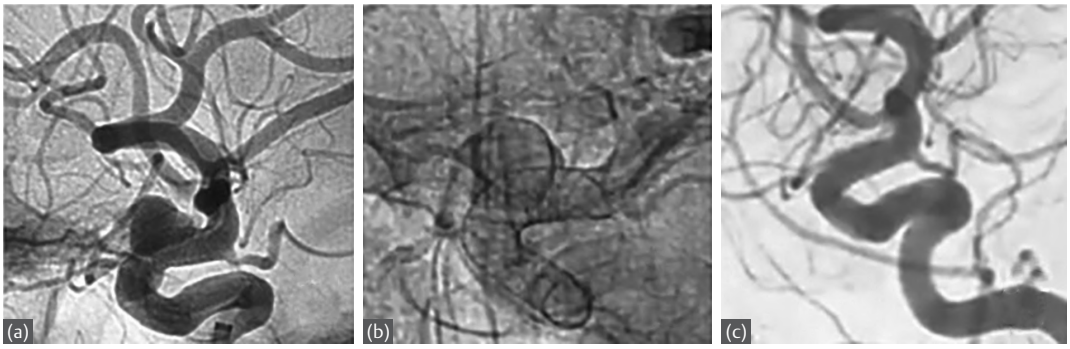

Fig. 1.4 **(a)** Ruptured, wide-neck, saccular paraophthalmic aneurysm. **(b)** Endoluminal reconstruction of the dysplastic vessel with a flow diverter. **(c)** Follow-up angiogram showing endothelialization of the flow diverter with complete exclusion of aneurysm from circulation.

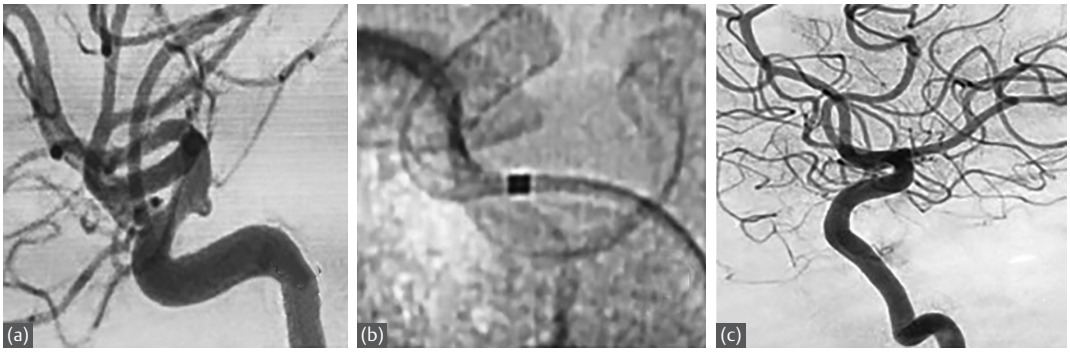

Fig. 1.5 **(a)** Ruptured blister aneurysm near posterior communicating artery. **(b)** Endoluminal reconstruction of the dysplastic vessel with a flow diverter. **(c)** Follow-up angiogram showing endothelialization of the flow diverter with complete exclusion of aneurysm from circulation.

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Nuances in FD Deployment

Triaxial Support System

We recommend a triaxial support system for FD deployment, so as to minimize "kick back" of the microcatheter while deploying the device, especially at sites like the internal carotid artery (ICA) bifurcation or while navigating the bends of the carotid siphon.

Wall Apposition

The FD braid strands serve as a scaffold for endothelial progenitor cells from the parent vessel, which migrate to form a nonpermeable tissue layer, effectively isolating the aneurysm from the blood circulation. This process of neo-endothelialization ensures that the aneurysm remains permanently excluded from the blood circulation. Good apposition of the device to the parent vessel walls is crucial, as the new endothelium primarily originates from migrating epithelial progenitor and smooth muscle cells through local paracrine signalling.[7] This explains the lower rates of aneurysm occlusion in fusiform and other nonsaccular aneurysms, where the device may not appose as closely to the vessel wall.[8]

If deemed necessary, balloon angioplasty should be used to ensure adequate wall apposition of the device.

Watch the Neck!

It seems like the most basic step; however, if not given adequate thought during the preprocedure planning in all the views (preferably three-dimensional rotational angiography), a part of the neck may remain uncovered, leading to various serious complications including re-rupture and residual remnants.

Device Size

Device diameter should be in accordance with the vessel lumen diameter (we recommend slightly oversizing by 0.5 mm), and device length should be adequate so as to cover the proximal and distal portions of the primary vessel beyond the aneurysm neck allowing device deployment without any tension and providing enough anchorage on both sides. Fusiform aneurysms may pose a unique challenge of shortening of the device length owing to the increased lumen diameter in the sac during deployment, so a device of the appropriate length should be selected taking this phenomenon into consideration.

Wait and Watch!

Ruptured aneurysms with significant subarachnoid hemorrhage (SAH) may render the access vessel into spasm. In such cases, nimodipine bolus/infusion and patience always help! Many times, the actual size of the aneurysm gets revealed once the spasm in the parent vessel is taken care of.

Challenges of Endoluminal Flow Diversion for Ruptured Aneurysms

Most commonly encountered complications of FD treatment are thromboembolic complications, delayed rupture of the aneurysm, and incomplete occlusion.[9]

Antiplatelet Strategy

Beyond acute ischemic and thromboembolic complications from in-stent macro thrombosis and occlusion, micro thrombus formation leads to uneven, heterogeneous neointimal formation and parent vessel stenosis.[10] Effective antiplatelet therapy is thus mandatory for all devices until neointimization occurs.

Dual antiplatelet therapy is recommended as loading dose predeployment of FDs in unruptured aneurysms and continued for at least 3 to 6 months followed by single

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antiplatelet for a year, until complete endothelialization occurs.[10] Although early studies typically employed aspirin and clopidogrel, prasugrel and ticagrelor represent alternatives that may reduce the incidence of antiplatelet resistance at a greater financial cost.[10] In practice, prasugrel is used predominantly in situations where the patient is a clopidogrel nonresponder.[11] Ticagrelor has been described as safe and efficacious in a series of neuroendovascular procedures as an alternative to clopidogrel, with loading doses of 180 mg and maintenance doses of 90 mg twice daily.[12]

In the setting of acute SAH and the use of FDs to treat ruptured aneurysms, there is still no consensus on the optimal antiplatelet drug regimen. In most centers, however, loading doses of clopidogrel and aspirin or ticagrelor are used. Typically, emergency loading doses in the range of 325 to 500 mg aspirin and 300 to 600 mg clopidogrel are administered at the time of, or up to 8 hours prior to, endovascular treatment. Both the drugs are then continued in lower maintenance doses from the day after treatment as for elective cases.[13,14]

We routinely use aspirin 300 mg and ticagrelor 180 mg loading at the time of induction of anesthesia for the procedure, and follow it up with aspirin 75 mg once daily along with ticagrelor 90 mg twice daily for 6 months, followed by aspirin monotherapy up to 1 year post-procedure. Gp IIb/IIIa inhibitors (tirofiban/eptifibatide) are used as bolus and infusion usually when thrombus formation is seen post device deployment on immediate/delayed runs.

There is insufficient evidence to broadly recommend platelet function testing when considering the robustness of the evidence. However, platelet function testing may play a role to guide care, particularly in cases where escalation or de-escalation of antiplatelet agents is necessary. Such guidelines have not been developed for patients undergoing neurointerventional procedures.[15]

Dual antiplatelet therapy in the acute period after SAH can complicate the management of hydrocephalus. New or worsening bleeding from aneurysm re-rupture or during procedures such as external ventricular drain or ventriculoperitoneal (VP) shunt placement can further complicate FD and post-deployment antiplatelet therapy.[16,17] We may have to reverse the effect of antiplatelet agents in case of life-threatening intracranial hematoma expansion, further increasing the risk of device-related thromboembolic complications.[18] Ticagrelor's reversibility and short half-life (7–8 h) may make this agent preferred over clopidogrel or prasugrel. There is a lack of data on the use of cangrelor, but its reversibility and short half-life (3–6 min) may prove useful in the setting of flow diversion for an acutely ruptured aneurysm.

Incomplete Occlusion and Delayed Rupture

Although intrasaccular stasis is often seen after the deployment of FDs, with rates of immediate complete angiographic occlusion of 14.5 to 32% in ruptured cases, there remains a period of time where the aneurysm remains at risk of re-rupture from incomplete dome protection and neointimal formation.[19,20]

Madaelil et al[21] published a meta-analysis of 126 ruptured IAs with rates of aneurysmal rebleeding after FD placement of 5% (6/126); sub-analysis showed re-rupture rates of only 2% (2/94) for IAs <2 cm. In a later 2018 meta-analysis of 223 patients undergoing FD treatment for IAs,[19] the re-rupture rate was 4%. Both meta-analyses found that re-rupture rates were highest during the first 24 to 72 hours after retreatment, and no rebleeding occurred after the first week following treatment. An updated 2022 meta-analysis of 318 FD-treated ruptured IAs[12] found pooled rates of rebleeding of up to 12%.

Latest Literature Review

The latest AHA/ASA guidelines (2023) suggest that the use of FDs should be avoided in the

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acute phase whenever a ruptured aneurysm can be treated (even partially to secure the rupture site) by primary coiling (including use of balloon-assisted techniques) or clipping due to the feared thromboembolic complications.[22,23] The "plug and pipe" staged treatment approach described by Howard et al has been tried in order to tide over the acute phase of SAH, where acute-phase coil embolization of ruptured IAs for dome protection is followed by delayed FD placement after acute SAH convalescence.[24]

In a meta-analysis[21] of case series and reports done in 2017, the composite rate of hemorrhagic or ischemic complications was 12% (15/126). Complete occlusion of the aneurysm was achieved in 90% (97/108) of the patients on follow-up imaging with a median angiographic follow-up of 6 months. They found that 81% of the patients with ruptured aneurysms treated with FDs had favorable clinical outcomes, which is comparable with the number of patients with similar outcomes in large trials such as International Subarachnoid Aneurysm Trial (ISAT). The overall improved angiographic and clinical outcomes in aneurysms of <7 mm suggest that FD-based treatment is more effective for small aneurysms. If larger aneurysms must be treated with FDs, then adjunctive coiling is likely worthwhile. They concluded that endovascular coil embolization and microsurgical clipping are likely to remain the first-line treatment of ruptured IAs, but when these options are not feasible, the use of FDs and appropriate dual antiplatelet therapy can allow a high rate of angiographic occlusion and a reasonable likelihood of good clinical outcome.

Jose et al[20] used FDs as monotherapy for the management of small-sized, wide-necked saccular aneurysms considered not amenable to, or high-risk for, coiling, blister aneurysms, and small dissecting or fusiform aneurysms. Procedural device-related clinical complications were recorded in six cases (7.9%) and resulted in permanent neurological morbidity in two (2.6%). No patient experienced aneurysm rebleeding or hemorrhagic complications attributed to the procedure during hospitalization, and there was no rebleeding during follow-up. Total or near-total occlusion was observed in 64/67 patients (95.5%) with 3- to 6-month follow-up digital subtraction angiography (DSA) and in all 71 cases evaluated at 12 months.[20]

Mokin et al[25] explored the use of FDs for ruptured blister aneurysms located at nonbranching segments of the supraclinoid ICA. They achieved complete obliteration in 87.5% (28/32) of aneurysms and reduced filling in 9.4% (3/32), with persistent filling in only 3.1% (1/32). There was no difference between aneurysm size (≤2 vs. >2 mm) or use of adjunct coiling and complete occlusion of the aneurysm on follow-up. At the 3-month follow-up, 81.3% (26/32) of the patients had an mRS score of 0 to 2. There were seven (16%) immediate procedural complications and two (5%) delayed complications, including a fatal delayed re-rupture after the initial treatment. Total or near-total occlusion was observed in 89.2% of patients at the 3- to 6-month angiographic follow-up and in 95.5% of cases evaluated at 10 to 14 months. Their results also support an FD treatment strategy for acutely ruptured blister aneurysms of the supraclinoid ICA.

Consistent occlusion rates ranging from 80 to 90% are reported in various recently published series,[26–28] thus favorably comparing to the results obtained in ruptured aneurysms treated with coiling.

Conclusion and the Future

Based on the current available literature, we can conclude that flow diversion in ruptured aneurysms in the acute stage is a valuable addition to our armamentarium of endovascular treatment strategies. They have made the surgeons' life easy in complex

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cases like wide-neck aneurysms, blister-like aneurysms, and fusiform and dissecting aneurysms.

Robotic-assisted neurovascular intervention is a nascent but rapidly expanding field.[29]

A limitation to understanding local gene and protein expression of the IA microenvironment has been the inability to obtain in vivo cerebrovascular specimens. Srinivasan et al provided an excellent review of the current state of transcriptomics, i.e., the study of protein expression, as a tool for understanding the FD microenvironment and it will assist in future research.[30]

Advances in FD technology, including surface coating with synthetic biocompatible polymers and resultant reduced thrombogenicity, may obviate the need for dual antiplatelet agents in patients treated with future generations of FDs.[31] Surface modification of metal devices and the future development of bioresorbable FDs (BRFDs) may ultimately lead to a lessened duration and magnitude (dual vs. single agent) of antiplatelet therapies in the future.[32]

Despite the significant advances made for the endovascular treatment of unruptured wide-neck aneurysms, many areas for technological and decision-making improvement exist. Clinical equipoise for wide-neck bifurcation aneurysms and ruptured aneurysms still exists.[33] The future possibilities of BRFDs, transcriptomics, and robotics systems for improved care are promising. The technological innovation of flow diversion for ruptured IAs is an ongoing phenomenon and future prospects look bright.

References

1. Wakhloo AK, Lieber BB. The Beginnings of Flow Diversion: A Historical Review. Flow Diversion of Cerebral Aneurysms. New York: Thieme; 2018
2. Campos JK, Cheaney Ii B, Lien BV, et al. Advances in endovascular aneurysm management: flow modulation techniques with braided mesh devices. Stroke Vasc Neurol 2020;5(1):1–13
3. Oliver AA, Senol YC, Bilgin C, et al. Intraluminal flow diverter design primer for neurointerventionalists. AJNR Am J Neuroradiol 2024;45(4):365–370
4. Lieber BB, Stancampiano AP, Wakhloo AK. Alteration of hemodynamics in aneurysm models by stenting: influence of stent porosity. Ann Biomed Eng 1997;25(3):460–469
5. Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, et al. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg 2021;13(1):54–62
6. Kallmes DF, Ding YH, Dai D, Kadirvel R, Lewis DA, Cloft HJ. A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. Stroke 2007;38(8):2346–2352
7. Rouchaud A, Ramana C, Brinjikji W, et al. Wall apposition is a key factor for aneurysm occlusion after flow diversion: a histologic evaluation in 41 rabbits. AJNR Am J Neuroradiol 2016;37(11):2087–2091
8. Foin N, Gutiérrez-Chico JL, Nakatani S, et al. Incomplete stent apposition causes high shear flow disturbances and delay in neointimal coverage as a function of strut to wall detachment distance: implications for the management of incomplete stent apposition. Circ Cardiovasc Interv 2014;7(2):180–189
9. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke 2013;44(2):442–447
10. Tonetti DA, Jankowitz BT, Gross BA. Antiplatelet therapy in flow diversion. Neurosurgery 2020; 86(Suppl 1):S47–S52
11. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5(12):2429–2436
12. Hanel RA, Taussky P, Dixon T, et al. Safety and efficacy of ticagrelor for neuroendovascular procedures. A single center initial experience. J Neurointerv Surg 2014;6(4):320–322
13. Delgado Almandoz JE, Crandall BM, Scholz JM, et al. Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. AJNR Am J Neuroradiol 2014;35(1):128–135

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14. Faught RW, Satti SR, Hurst RW, Pukenas BA, Smith MJ. Heterogeneous practice patterns regarding antiplatelet medications for neuroendovascular stenting in the USA: a multicenter survey. J Neurointerv Surg 2014;6(10):774–779
15. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12(16):1521–1537
16. Mahaney KB, Chalouhi N, Viljoen S, et al. Risk of hemorrhagic complication associated with ventriculoperitoneal shunt placement in aneurysmal subarachnoid hemorrhage patients on dual antiplatelet therapy. J Neurosurg 2013;119(4):937–942
17. Ospel JM, Brouwer P, Dorn F, et al. Antiplatelet management for stent-assisted coiling and flow diversion of ruptured intracranial aneurysms: a DELPHI consensus statement. AJNR Am J Neuroradiol 2020;41(10):1856–1862
18. Kung DK, Policeni BA, Capuano AW, et al. Risk of ventriculostomy-related hemorrhage in patients with acutely ruptured aneurysms treated using stent-assisted coiling. J Neurosurg 2011;114(4): 1021–1027
19. Cagnazzo F, di Carlo DT, Cappucci M, Lefevre PH, Costalat V, Perrini P. Acutely ruptured intracranial aneurysms treated with flow-diverter stents: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2018;39(9):1669–1675
20. Cohen JE, Gomori JM, Moscovici S, et al. Flow-diverter stents in the early management of acutely ruptured brain aneurysms: effective rebleeding protection with low thromboembolic complications. J Neurosurg 2021;135(5): 1394–1401
21. Madaelil TP, Moran CJ, Cross DT III, Kansagra AP. Flow diversion in ruptured intracranial aneurysms: a meta-analysis. AJNR Am J Neuroradiol 2017; 38(3):590–595
22. Giorgianni A, Agosti E, Molinaro S, et al. Flow diversion for acutely ruptured intracranial aneurysms treatment: a retrospective study and literature review. J Stroke Cerebrovasc Dis 2022; 31(3):106284
23. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke 2023;54(7):e314–e370
24. Howard BM, Frerich JM, Madaelil TP, et al. "Plug and pipe" strategy for treatment of ruptured intracranial aneurysms. J Neurointerv Surg 2019; 11(1):43–48
25. Mokin M, Chinea A, Primiani CT, et al. Treatment of blood blister aneurysms of the internal carotid artery with flow diversion. J Neurointerv Surg 2018;10(11):1074–1078
26. Goertz L, Dorn F, Kraus B, et al. Safety and efficacy of the Derivo Embolization Device for the treatment of ruptured intracranial aneurysms. J Neurointerv Surg 2019;11(3):290–295
27. Lozupone E, Piano M, Valvassori L, et al. Flow diverter devices in ruptured intracranial aneurysms: a single-center experience. J Neurosurg 2018;128(4):1037–1043
28. Mahajan A, Das B, Narang KS, et al. Surpass flow diverter in the treatment of ruptured intracranial aneurysms—a single-center experience. World Neurosurg 2018;120:e1061–e1070
29. Mendes Pereira V, Rice H, De Villiers L, et al. Evaluation of effectiveness and safety of the CorPath GRX robotic system in endovascular embolization procedures of cerebral aneurysms. J Neurointerv Surg 2024;16(4):405–411
30. Srinivasan VM, Shekhtman O, Kandregula S, Mannam SS, Yu LFC, Kan P. Transcriptomics of intracranial aneurysms: current state and opportunities in flow diversion. J Neurosurg 2023; 140(5):1335–1343
31. Manning NW, Cheung A, Phillips TJ, Wenderoth JD. Pipeline shield with single antiplatelet therapy in aneurysmal subarachnoid haemorrhage: multicentre experience. J Neurointerv Surg 2019; 11(7):694–698
32. Oliver AA, Carlson KD, Bilgin C, et al. Bioresorbable flow diverters for the treatment of intracranial aneurysms: review of current literature and future directions. J Neurointerv Surg 2023;15(2):178–182
33. Mascitelli JR. Management of wide-neck aneurysms in 2024: how does one make the best treatment decision when there are so many good options? J Neurointerv Surg 2024;16(5):433–434

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2 Incidental Gliomas

Krishnamurthy Sridhar, Siddarth Kannan, and Ashwin Sridhar

Definition

Gliomas classically present with symptoms of seizures, headache, and/or focal neurological deficits. Rarely, gliomas may be found incidentally when MRI is performed for reasons other than specific symptoms related to a tumor, related to trauma, medical checkup, otological studies, and the like. An "incidental" finding was defined as an abnormality on imaging that was obtained for a reason not attributable to the glioma, such as trauma, headache, screening, or research participation.[1] These incidental gliomas are most often low grade gliomas (iLGG) and constitute about 10% of all low-grade gliomas (LGGs) and about 0.04 to 0.2% in the general population.[2] They are characterized by a slow and indolent growth over a long period of time.[3–5] An increasing use of MRI for a variety of reasons has increased the likelihood of finding iLGG.[6] In a study of 72 patients, the most common presenting symptom was headache (50%), followed by dizziness (22%) and mood disorders (8%). Other reported nonspecific or unrelated symptoms included amenorrhea (6%), blurred vision (4%), fainting (4%), hearing deficiencies (4%), and lower-limb paresthesia (2%).[6]

Gliomas exhibit four stages in their evolution: (1) the occult stage, where they are asymptomatic and not detected on MRI; (2) incidental stage, where the patient is asymptomatic and the lesion is incidentally detected on MRI; (3) symptomatic stage; and (4) malignant transformation stage.[7] Incidental gliomas most often lack the classical histological features of malignant gliomas and are most often classified into WHO grades 1 and 2 astrocytoma, oligodendroglioma, and ganglioglioma. Molecular typing of the iLGG has also shown no major difference to LGG with a majority being IDH mutant and with 1p19q mutations.[7]

The reason for the asymptomatic nature of the tumor could probably be the significantly lower preoperative tumor volumes of iLGG as well as the significantly younger age at the time of surgery, which could be related to the fact that tumor had less time to grow and therefore did not reach the significant volume to cause symptoms.[8–10]

Radiological Features

An increasing utilization of the MRI as a screening tool for many neurological symptoms has increased the incidence of discovery of iLGG. Most LGGs present as isointense or hypointense on T1-weighted and hyperintense on T2-weighted MRIs (**Fig. 2.1**). They are not usually contrast-enhancing lesions.[11] The use of advanced imaging with MR sequences like perfusion, diffusion-weighted imaging, and diffusion tensor imaging all contribute to the definitive diagnosis of an iLGG. Subtle imaging changes reflect tumor growth. LGGs demonstrate a spontaneous velocity of diametric expansion of 4 mm/year before and after surgical resection.[12,13] The changes seen in tumor growth kinetics before and after surgery reflect the aggressiveness of the lesion even in iLGG.[10]

Management

Surgery remains the first line of treatment in the management of any brain tumor, with the extent of resection (EOR) having a direct correlation to the overall survival (OS). However, in the case of iLGG, there has been a debate based on medical and ethical issues. Historically, a wait-and-see strategy has

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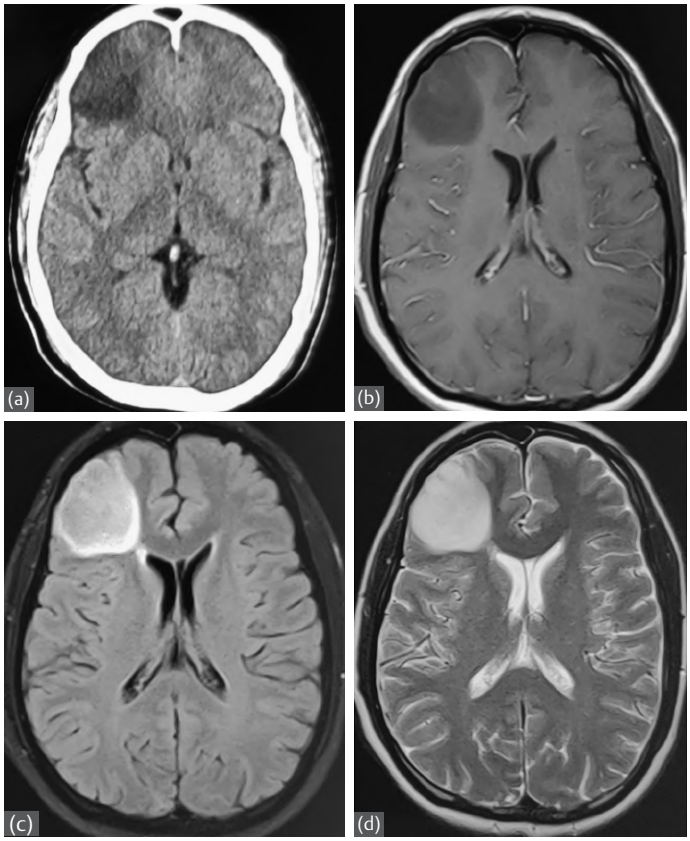

Fig. 2.1 A 37-year-old male presented with headaches. **(a)** CT scan of brain showed a circumscribed right frontal hypodense lesion. **(b–d)** The MRI scan was typical for a low-grade glioma with a right, frontal, circumscribed, non-enhancing lesion hypointense on T1-weighted and hypointense on T2-weighted sequences. The fluid-attenuated inversion recovery (FLAIR) sequence showed minimal surrounding hyperintensity going toward the frontal horn. Radical excision was done. The pathology of Grade II low-grade lesion with IDH positivity was confirmed. The excision was followed up with radiation and temozolomide.

often been chosen until the patients become symptomatic or the radiology on follow-up shows signs of malignant transformation like contrast enhancement.[14] There has been a growing consensus among neurosurgeons that these tumors are not as indolent as originally characterized to be but instead are tumors that carry a risk of progression to a higher grade and possible anaplastic transformation resulting in death. The incidence of progression is highly variable, ranging from 17 to 73%, and the reported median interval is between 2 and 10 years.[15] It has also been suggested that as gliomas spread by infiltration along white matter tracts, it is important to study the infiltration of the adjacent tracts to determine the timing of surgery and the prognosis.[16]

Zeng et al reported an intriguing comparison of surgical timing between two cohorts of iLGG patients: (1) those who underwent surgical resection prior to symptom onset and (2) those who delayed surgical treatment until symptoms arose. This study found that surgical timing was not significantly associated with OS, progression-free survival (PFS), and malignant PFS (MPFS) rates, while total resection was a significant factor that showed positive correlation to OS, PFS, and MPFS. The authors therefore concluded that surgical timing should be utilized to assist neurosurgeons with achieving maximal EOR.[17]

Jakola et al and Ius et al noted better OS in patients with LGG and iLGG undergoing early resection compared to those managed conservatively (including biopsy and "wait and see" approach).[18,19] Allison et al looking at the 20 iLGG of the 150 total LGG found improved PFS and OS following gross total removal

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versus the biopsy group.[20] The postoperatively better Eastern Cooperative Oncology Group (ECOG) performance score demonstrated that surgical treatment can be performed safely particularly in asymptomatic patients with no higher risk of postoperative complications or permanent neurological deficits.[8] Although some groups have shared concern about sacrificing cognitive function in young patients with iLGGs for early resection, recent data shows neuropsychological results were not impacted by awake surgery.[21] Birladeanu et al looked at the 11 patients with iLGG versus the symptomatic LGG (sLGG) in their study and found that their data supported safety and effectiveness of early surgery for iLGG.[22] Yang et al looked at the morphological data of the corticospinal tract in incidental versus symptomatic insular gliomas and concluded that even if incidental cases experience motor impairments, they may recover motor function more quickly during subsequent rehabilitation compared to symptomatic cases.[23]

Ius et al looked at the benefit of early surgery in 297 patients in a multicenter study. Their results showed a 10-year OS rate of 93.2%, which was significantly higher than that for sLGG.[19] The preoperative tumor volume was the only predictor of OS and was negatively associated with the EOR. The tumor recurrence, seen in 38.7%, was associated with early surgery and highlighted the fact that iLGG is not an indolent and benign pathology. The authors also felt that the fact that as iLGGs are smaller than sLGGs, either total or supratotal resection becomes safer and/or more feasible, and in turn gives improved outcomes shown with gross total or better resections.

Demetz et al looked at differences in molecular characteristics between iLGG and sLGG.[8] A total of 161 patients were enrolled in the study of which 23 were identified as iLGG. The iLGG demonstrated significantly more favorable characteristics, such as IDH1 mutation, lack of anaplasia, and lower mitotic rates in the incidental group compared to the symptomatic group. The already described characteristics for iLGG such as younger age, better ECOG performance, smaller preoperative tumor volumes, higher EOR, and better PFS and OS were also confirmed by the study. Ius et al found that the IDH wild type patients in their study had a surprisingly good prognosis without a single death in the follow-up period.[19] This good prognosis is especially true if they have a TERT promoter mutation in addition.

Favorable molecular, neuropathological, epidemiological, radiological, and surgical characteristics lead to a significantly better PFS and OS in patients with iLGG.[24] There is an almost seven times higher hazard for earlier progression and an almost a five times higher hazard for shorter OS in patients with sLGG compared to patients with iLGG. This could be of clinical relevance, helping the treating physicians to explain the patients the benefits of a treatment even at an asymptomatic stage. The better PFS and OS mandate not only for early maximum safe resection in iLGG, but also strongly argues against a wait and see strategy, which was historically justified by the generally slow growth of LGG and the risk of postoperative deficits.

Studies have suggested a higher incidence of total as well as supramarginal resection in iLGG because of the lower tumor volume and lower risk of eloquent tumor location. With an increasing number of studies which suggest a more aggressive surgical strategy aiming to resect the peri-tumoral infiltrated areas as well, iLGG could benefit from their lower incidence of non-eloquent tumor location, since the higher EOR could also be translated into a longer PFS and OS.[25] In these circumstances, a decision to observe and withhold surgery in a patient with iLGG may be difficult to understand and explain to a patient, as there is currently increasing evidence that surgical excision is safe and of benefit to the patient in OS.[19,26]

There is no current consensus on the role of postsurgical adjuvant radiation or chemotherapy. Regular follow-up of these

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patients may reveal growth of the residual lesion or a recurrence, when an individualized multidisciplinary approach has been advocated.[19] Ius et al found tumor recurrence in 108 of 259 patients (40.44%) with an estimated recurrence rate at 5 and 10 years of 36.9 and 57.7%, respectively.[19] At recurrence a surgical option is considered first if there is a reasonable chance of total or near-total excision. Rarely, an initial chemotherapy has been advocated as presurgical therapy in some patients.[27]

Conclusion

Incidental gliomas are rare pathologies but which are increasingly diagnosed because of the increasing use of MRI in the management of other neurological symptoms as well as for research. Most often these are low-grade lesions. However, there is evidence that these do progress and can transform into higher grade lesions. Advanced MRI is of considerable help in the characterization of these lesions and in the surgical decision-making. It is now evident that a "wait and watch" policy is not beneficial to the patient. Early surgery provides an opportunity for radical and occasional supramarginal excision with improved recurrence-free and OS rates. It has also been noted that even where postoperative functional morbidity is seen, this often recovers as there is minimal involvement of the adjacent white matter tracts.

References

1. Opoku-Darko M, Lang ST, Artindale J, Cairncross JG, Sevick RJ, Kelly JJP. Surgical management of incidentally discovered diffusely infiltrating low-grade glioma. J Neurosurg 2018;129(1):19–26
2. Eskandary H, Sabba M, Khajehpour F, Eskandari M. Incidental findings in brain computed tomography scans of 3000 head trauma patients. Surg Neurol 2005;63(6):550–553, discussion 553
3. Pallud J, Capelle L, Taillandier L, Badoual M, Duffau H, Mandonnet E. The silent phase of diffuse low-grade gliomas. Is it when we missed the action? Acta Neurochir (Wien) 2013;155(12):2237–2242
4. Pallud J, Mandonnet E. Incidental low-grade gliomas. J Neurosurg 2013;118(3):702–704
5. Mandonnet E, de Witt Hamer P, Pallud J, Bauchet L, Whittle I, Duffau H. Silent diffuse low-grade glioma: toward screening and preventive treatment? Cancer 2014;120(12):1758–1762
6. Shah AH, Madhavan K, Heros D, et al. The management of incidental low-grade gliomas using magnetic resonance imaging: systematic review and optimal treatment paradigm. Neurosurg Focus 2011;31(6):E12
7. Pradhan A, Mozaffari K, Ghodrati F, Everson RG, Yang I. Modern surgical management of incidental gliomas. J Neurooncol 2022;159(1):81–94
8. Demetz M, Krigers A, Moser P, Kerschbaumer J, Thomé C, Freyschlag CF. Same but different. Incidental and symptomatic lower grade gliomas show differences in molecular features and survival. J Neurooncol 2023;162(2):397–405
9. Pallud J, Fontaine D, Duffau H, et al. Natural history of incidental World Health Organization grade II gliomas. Ann Neurol 2010;68(5):727–733
10. Pallud J, Blonski M, Mandonnet E, et al. Velocity of tumor spontaneous expansion predicts long-term outcomes for diffuse low-grade gliomas. Neuro-oncol 2013;15(5):595–606
11. Bai J, Varghese J, Jain R. Adult glioma WHO classification update, genomics, and imaging: what the radiologists need to know. Top Magn Reson Imaging 2020;29(2):71–82
12. Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol 2003;53(4):524–528
13. Mandonnet E, Pallud J, Fontaine D, et al. Inter- and intrapatients comparison of WHO grade II glioma kinetics before and after surgical resection. Neurosurg Rev 2010;33(1):91–96
14. Cochereau J, Herbet G, Rigau V, Duffau H. Acute progression of untreated incidental WHO Grade II glioma to glioblastoma in an asymptomatic patient. J Neurosurg 2016;124(1):141–145
15. Noorani I, Sanai N. Surgical management of incidental gliomas. Neurosurg Clin N Am 2017;28(3):397–406
16. Duffau H. White matter tracts and diffuse lower-grade gliomas: the pivotal role of myelin plasticity in the tumor pathogenesis, infiltration

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patterns, functional consequences and therapeutic management. Front Oncol 2022;12:855587
17. Zeng L, Mei Q, Li H, Ke C, Yu J, Chen J. A survival analysis of surgically treated incidental low-grade glioma patients. Sci Rep 2021;11(1):8522
18. Jakola AS, Myrmel KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA 2012;308(18):1881–1888
19. Ius T, Ng S, Young JS, et al. The benefit of early surgery on overall survival in incidental low-grade glioma patients: a multicenter study. Neuro-oncol 2022;24(4):624–638
20. Allison CM, Shumon S, Stummer W, Holling M, Surash S. A cohort analysis of truly incidental low-grade gliomas. World Neurosurg 2022;159: e347–e355
21. Ng S, Herbet G, Lemaitre AL, Cochereau J, Moritz-Gasser S, Duffau H. Neuropsychological assessments before and after awake surgery for incidental low-grade gliomas. J Neurosurg 2020; 135(3):871–880
22. Birladeanu A, Barberis M, Poisson I, Froelich S, Mandonnet E. Oncological and functional outcomes support early resection of incidental IDH-mutated glioma. Acta Neurochir (Wien) 2023;165(10):2755–2767
23. Yang ZC, Yin CD, Yeh FC, et al. A preliminary study on corticospinal tract morphology in incidental and symptomatic insular low-grade glioma: implications for post-surgical motor outcomes. Neuroimage Clin 2023;40:103521
24. Lima GLO, Dezamis E, Corns R, et al. Surgical resection of incidental diffuse gliomas involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie 2017;63(3):250–258
25. Park J, Sim J, Ahn J, et al. Molecular characteristics of incidental lower-grade glioma for treatment decision-making. J Neurosurg 2022;138(3): 629–638
26. Aghi MK, Nahed BV, Sloan AE, Ryken TC, Kalkanis SN, Olson JJ. The role of surgery in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2015; 125(3):503–530
27. Blonski M, Taillandier L, Herbet G, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. J Neurooncol 2012;106(2):353–366

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3 Deep Brain Stimulation in Early Parkinson's Disease Is Useful

Hrishikesh Kumar, Debapriya Mukherjee, and Jacky Ganguly

Introduction

Parkinson's disease (PD) is second most common neurodegenerative disorder with global prevalence of about 150 per 100,000 population. The cardinal symptoms of PD are bradykinesia, rigidity, rest tremor, and postural imbalance.[1] Apart from these motor symptoms, PD patients present with nonmotor symptoms like cognitive decline, neuropsychiatric symptoms, urinary problem, pain, hyposmia, and sleep disorders (especially REM sleep behavior disorders where patients enact the dream during sleep).[2]

The underlying pathology of PD is nigrostriatal degeneration related to misfolded synuclein, resulting in dopaminergic deficiency. There are various other proposed patho-mechanisms like inflammation, and lysosomal and mitochondrial dysfunction. Dopamine replacement therapy in the form or oral levodopa has remained the core of pharmacological treatment—it has changed the face of treatment of PD. PD is the only neurodegenerative condition where pharmacological treatment results in substantial symptomatic benefit. Patients exhibit dramatic response to levodopa, but the response does not last for more than few hours. With passage of time, the duration of response to levodopa shrinks and patients develop motor fluctuations (on–off phenomenon and dyskinesia). Advent of deep brain stimulation (DBS) surgery has been a game changer in addressing the issue of motor fluctuation.[3,4] Subthalamic nucleus, globus pallidus, and thalamus are the targets of neurostimulation, depending upon the patient population, presentation, and experience of the center.[5,6]

Selection of candidates for DBS is the most important step to ensure the surgical benefit. The selection has traditionally been based on recommendation by Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT PD). With increasing experience with DBS, subsequent modifications are incorporated into clinical practice.[7] An ideal candidate of DBS surgery would be:

- Unequivocal diagnosis of PD.
- Excellent response to levodopa.
- Motor fluctuation with levodopa.
- Less than 75 years old.
- At least 5 years of disease.
- No cognitive decline or no significant neuropsychiatric symptoms.
- No significant comorbidities.

Patients with poor balance, significant cognitive decline, and speech and gait symptoms persisting during levodopa on phase are not good candidates for DBS surgery.[8]

Each of the above criteria deserves further elaboration which may be out of scope for this chapter. Response to levodopa has been the key for case selection. In best case scenario, DBS surgery is expected to provide symptom relief similar to levodopa on phase without dyskinesia and motor fluctuation.[9] This implies that those patients who don't have good "ON" with levodopa generally don't do well on DBS.

As levodopa responsiveness is key to predict the effect of DBS, it becomes imperative to record the response to levodopa in an objective manner. Levodopa challenge test (LCT) provides this objective evidence of levodopa responsiveness.[10] In LCT, motor Unified Parkinson's Disease Rating Scale (UPDRS) score

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is performed in the morning off phase and then again in on phase (after taking 1.5 to 2 times the usual morning oral dose of levodopa). A difference of more than 30% in UPDRS motor score indicates adequate levodopa response and these patients are expected to do well after DBS surgery. There are exceptions where we may not find this degree of improvement on LCT but still patients respond well to DBS surgery. The exceptions are tremor dominant PD where tremor is quite significant. These patients may not respond well to levodopa but can do well with DBS. Another exception is subgroup of patients having freezing of gait during off phase and remarkable improvement with levodopa. Such patients walk well after taking levodopa but overall change in UPDRS score may be less than 30%. These patients generally do well on DBS as freezing is the main symptom that improves.[11] Another criterion of cut-off age of 70 or 75 is also contentious. Many patients more than 70 or 75 years of age may be physically and mentally fit with no comorbidities. Reasonably good response to DBS has been reported in up to 80 years of age.[12–14] Obviously, no criterion is absolute for patient selection and all the patients should be evaluated individually.

The most debated aspect of case selection is when to offer surgery (how long after onset of disease). One may argue that this itself is a moot point as it is difficult to ascertain the real onset of PD in any patient. Neurodegeneration starts long before the onset of motor symptoms. Some of the nonmotor symptoms (like REM sleep behavior disorder or hyposmia) predates onset of motor symptoms by years. But as DBS is supposed to help motor symptoms, a practical guide about when to offer surgery must be linked with onset and present state of motor symptoms.

When DBS surgery presented itself as an option, it was offered for advanced PD (usually into 11 years of disease or more). But delaying DBS surgery for this long implied that many patients already had significant motor fluctuation. This delay had the potential of missed years when patients' quality of life could have been much better. Delayed surgery also meant suboptimal benefit even after performing surgery.

The reasons put forward in favor of delaying DBS can be debated:

- Possibility of atypical Parkinsonism: During the initial years, atypical Parkinsonism may look and behave like PD and even respond to levodopa. After a few years of onset of motor symptoms, the features of atypical Parkinsonism become more obvious. This is especially true for multi-system atrophy–Parkinsonian type (MSA-P) or progressive supranuclear palsy–Parkinsonism (PSP-P). Performing DBS early in the course of disease may lead to surgery in some patients with atypical Parkinsonism. This is undesirable as the disease course in atypical Parkinsonism would be downhill and symptoms would be resistant to DBS.[15] How long one can wait for appearance of features of atypical Parkinsonism (if at all they appear) is unclear. Generally, patients exhibit signs of atypical Parkinsonism latest by 5 years of onset of motor symptoms.
- Best medical treatment sufficient: If the patient is already doing well on 3 to 4 times of levodopa and have minimal motor fluctuation, performing DBS may sound overzealous at that point in time. The possible risk of surgery may not be worth taking at that point in time as surgery would hardly add any symptomatic benefit over the best medical treatment at that point in time.

On the other hand, there are arguments in favor of performing early surgery. It is well known that continuous dopaminergic stimulation delays the motor fluctuation. Thus, performing surgery early may delay the motor fluctuation and provide better functional life especially in younger patients. Moreover,

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there are early evidences that DBS imparts some neuroprotection.[16]

Before we discuss further about these points, we must make it clear what exactly early PD means? Early stage of PD has been described variously—a timeline of 4 years, 5 years, or even 7 years since the onset of symptoms has been considered as early PD. One should be aware that this duration criterion for defining early PD has its own fault line. There are patients who progress faster and by 5 years, symptoms are significant (Hoehn and Yahr stage 3 or more). On the other hand, there are patients who stay relatively well for almost a decade or more since the onset of motor symptoms. A rational way to address this dilemma would be to consider early PD till the patients have good levodopa on period and have developed early motor complications; this generally coincides with the duration of 4 to 7 years after the onset of motor symptoms.

Considering DBS in early PD might feel counterintuitive as patients generally are doing well on medicines, but let us examine two arguments that have been put forward to offer surgery in early PD. Incidentally, both these arguments are not exclusive, and they are linked to each other.

- Delay in disease progression milestones: There are ample evidence that DBS provides better motor control than best medical treatment and the effect is sustained for 5 to 10 years.[5,17] It also helps in reducing the medication load and subsequently medication-induced side effects. After surgery, patients often experience a stage of "DBS-honeymoon phase" akin to levodopa honeymoon phase when levodopa is started.[18] Whether this improvement translates into delaying late-stage disability milestones like falls, psychosis, institutionalization, and survival is unclear. There are indications from controlled, long-term observational studies that there is delay in these milestones, but we can get clear answer to these fundamental questions by randomized controlled trials of early versus late DBS separated by sufficient delay and by DBS versus best medical treatment with longer follow-ups. Evidently, conducting such trials would be extremely challenging.
- Evidence of DBS-induced neuroprotection in animal: Chronic Subthalamic Nucleus (STN) stimulation in rodent models of PD (6-hydroxydopamine (6-OHDA) administered) was shown to protect dopaminergic neurons in substantia nigra.[19] STN stimulation has also shown to limit dopaminergic loss in the substantia nigra and periaqueductal gray of primate PD models (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated). Importantly, less neuronal rescue was found in animals with more severe lesion. This indicates that the stimulation may only protect the neurons from milder form of neurotoxicity and there may be a threshold of neurodegeneration after which the neuroprotective effect of DBS may not work. One may assume that DBS may lead to neuroprotection when performed in very early PD or during pre-motor phase of PD. Having a trial of DBS at this stage will be ethically not possible considering the inherent adverse effect of any surgery. Moreover, there would always be doubt about translational value of such animal studies because of acute nature of insult in such model and absence of key neuropathological features found in humans (notably synucleinopathy).

EARLYSTIM Trial Findings

There have been many clinical studies over the last two decades that have tried to compare results between early DBS and best medical therapy. The EARLYSTIM trial involved a random assignment of 251 PD patients with

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early motor complication into DBS plus medical therapy and only medical therapy groups.[5] They were 4 years or more (mean 7.5 years) into the disease. The intervention group fared better than medical therapy group in terms of motor disability, activity of daily living, levodopa-induced motor complications, and time with good mobility without dyskinesia. Adverse effect as compared to medical therapy group was not too different. Another 5 years follow-up study of DBS in early PD suggested that early DBS reduced the need for and complexity of PD medications while providing long-term motor benefit over best medical therapy.[17]

Based on the EARLYSTIM data, FDA approved use of DBS in people with PD of at least 4 years duration and with recent onset motor complications or motor complications of longer-standing duration that are not adequately controlled with medication.

Conclusion

There is undeniable evidence that DBS surgery in PD with early motor complications provides benefit over only medical therapy. But it remains doubtful that this evidence should change our practice completely and we start offering DBS in all early PD patients.[20] As far as the present understanding, each case should be analyzed individually, and multiple factors should be taken into account. The decision for or against DBS in early PD should be based on the age of the patient, nature of job of the patient, expectation, surgical risk, presence or absence of red flags of atypical Parkinsonism, clinical course in individual patient, and socioeconomic factors. It is possible that future studies will unfold more clear answer.

References

1. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51(6):745–752
2. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol 2008;15(Suppl 1):14–20
3. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8(1):67–81
4. Mahlknecht P, Foltynie T, Limousin P, Poewe W. How does deep brain stimulation change the course of Parkinson's disease? Mov Disord 2022;37(8): 1581–1592
5. Schuepbach WMM, Rau J, Knudsen K, et al; EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368(7):610–622
6. Hariz M, Blomstedt P. Deep brain stimulation for Parkinson's disease. J Intern Med 2022;292(5): 764–778
7. Artusi CA, Lopiano L, Morgante F. Deep brain stimulation selection criteria for Parkinson's disease: time to go beyond CAPSIT-PD. J Clin Med 2020;9(12):3931
8. Munhoz RP, Picillo M, Fox SH, et al. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. Can J Neurol Sci 2016;43(4):462–471
9. Su D, Chen H, Hu W, et al. Frequency-dependent effects of subthalamic deep brain stimulation on motor symptoms in Parkinson's disease: a meta-analysis of controlled trials. Sci Rep 2018;8(1): 14456
10. Saranza G, Lang AE. Levodopa challenge test: indications, protocol, and guide. J Neurol 2021; 268(9):3135–3143
11. Huang C, Chu H, Zhang Y, Wang X. Deep brain stimulation to alleviate freezing of GAIT and cognitive dysfunction in Parkinson's disease: update on current research and future perspectives. Front Neurosci 2018;12:29
12. Jiang C, Wang J, Chen T, Li X, Cui Z. Short- and long-term efficacy and safety of deep-brain stimulation in Parkinson's disease patients aged 75 years and older. Brain Sci 2022;12(11):1588
13. Sharma VD, Lyons KE, Nazzaro JM, Pahwa R. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease patients over 75 years of age. J Neurol Sci 2019;399:57–60
14. Mathkour M, Garces J, Scullen T, et al. Short- and long-term outcomes of deep brain stimulation in patients 70 years and older with Parkinson disease. World Neurosurg 2017;97:247–252

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15. Artusi CA, Rinaldi D, Balestrino R, Lopiano L. Deep brain stimulation for atypical parkinsonism: a systematic review on efficacy and safety. Parkinsonism Relat Disord 2022;96:109–118
16. McKinnon C, Gros P, Lee DJ, et al. Deep brain stimulation: potential for neuroprotection. Ann Clin Transl Neurol 2018;6(1):174–185
17. Hacker ML, Turchan M, Heusinkveld LE, et al. Deep brain stimulation in early-stage Parkinson disease: five-year outcomes. Neurology 2020; 95(4):e393–e401
18. Muthuraman M, Koirala N, Ciolac D, et al. Deep brain stimulation and L-DOPA therapy: concepts of action and clinical applications in Parkinson's disease. Front Neurol 2018;9(711):1-16
19. Knorr S, Musacchio T, Paulat R, et al. Experimental deep brain stimulation in rodent models of movement disorders. Exp Neurol 2022;348: 113926
20. Cabrera LY, Goudreau J, Sidiropoulos C. Critical appraisal of the recent US FDA approval for earlier DBS intervention. Neurology 2018;91(3):133–136

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4 Medication-Overuse Headache: Detoxification Is the Key

Navendu N. Jana, Arindam Ghosh, Arindam Das, and Pahari Ghosh

Introduction

Medication-overuse headache (MOH) is a headache that affects patients afflicted with a primary headache disorder, but is a headache for the treating physician or neurologist as well, and has been so for most of the last century. MOH is perhaps the most common "Catch-22" situation that involves a headache specialty practice. It is characterized as a nearly daily headache in patients with pre-existing primary headache disorders who are overusing one or more rescue medications for symptoms. This chapter reviews MOH in reference to the latest International Classification of Headache Disorders criteria (ICHD-3) viewed as a secondary headache and is often felt to be the most common cause of the development of chronic migraine.[1]

History

MOH was probably described first in German medical literature in the early 1900s but was not widely known due to paucity of literature in English. Gradually the rampant use of abortive medications containing ergot to treat migraine was recognized as a trigger of chronic migraine and multiple authors including Graham, Friedman, Lennox, and later Horton and Peters gave detailed descriptions.[2] Use of other abortive medications especially in combination with ergotamine was also recognized as a cause of chronic headache and was termed as *analgesic rebound headache* in the 1980s.[3] As the armamentarium for rescue medications for headache especially migraine grew, the prevalence of MOH grew symbiotically.

Epidemiology

MOH is uncommon in population ranging from 0.5 to 7.2%[4] but is substantial in specialized headache clinics. Prevalence also differs depending on the offending drug with observations that opioids, barbiturates, and combination analgesics cause more cases than triptans. It has also been observed that MOH is seen more in migraine compared to tension or cluster headaches. Existence of stress personality traits further contributes to the prevalence. Other factors are extremes of socioeconomic status, multiple comorbidities, and level of education.

ICHD-3 Diagnostic Criteria

Medication-overuse headache

Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder.

Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

Not better accounted for by another ICHD-3 diagnosis.

Classification of headache according to the overused drug

Ergotamine-overuse headache: Headache occurring on ≥15 days/month as a consequence of regular use of ergotamine on ≥10 days/month for >3 months.

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Triptan-overuse headache: Headache occurring on ≥15 days/month as a consequence of regular use of triptans on ≥10 days/month for >3 months.

Nonopioid analgesic–overuse headache: Headache occurring on ≥15 days/month as a consequence of regular use of paracetamol, NSAIDs, acetylsalicylic acid, or other nonopioid analgesics on ≥15 days/month for >months.

Opioid-overuse headache: Headache occurring on ≥15 days/month as a consequence of regular use of opioids on ≥10 days/month for >3 months.

Combination analgesic–overuse headache: Headache occurring on ≥15 days/month as a consequence of regular use of combination analgesics on ≥10 days/month for >3 months. The term "combination analgesics" refers to formulations combining analgesic drugs from different classes (for example, paracetamol and codeine) or analgesics with drugs acting as adjuvants (for example, caffeine).

Medication-overuse headache attributed to multiple drug classes not individually overused: Headache occurring on ≥15 days/month as a consequence of regular intake of any combination of ergotamine, triptans, nonopioid analgesics, or opioids on a total of ≥10 days/month for >3 months, without overuse of any single drug or drug class alone.

Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes: Headache occurring on ≥15 days/month as a consequence of regular intake of any combination of ergotamine, triptans, nonopioid analgesics, and/or opioids on ≥10 days/month for >3 months (the identity, quantity, and/or pattern of use of overuse of these classes of drugs cannot be reliably established).

Medication-overuse headache attributed to other medication: Headache occurring on ≥15 days/month as a consequence of regular intake of one or more medications other than those described above on 10 days/month for >3 months.

ICHD-3, International Classification of Headache Disorders, 3rd edition; NSAID, non-steroidal anti-inflammatory drug.

Source: Reproduced with permission of International Headache Society.

Substance Abuse and MOH—Two Sides of the Same Coin?

There is no doubt that MOH shares features of substance use.[5] About 50% of patients with MOH fulfilled the criteria of substance abuse according to DSM IV. Withdrawal symptoms are a characteristic of both along with inability to reduce consumption and unfortunately high rates of relapse.

Central Sensitization

One possible mechanism of chronification of headache is central sensitization. Pathophysiology involves continuous alterations in dural afferent fibers, nitric oxide synthase, and calcitonin-related peptide.[6] Although detoxification may take up to a year, MOH-related pain hyperexcitability is reversible, and here lies the importance of preventing relapses in these patients.[7]

Clinical Characteristics

It is understandable that the diagnosis is a clinical one. Baseline features will be similar to the pre-existing primary headache. However, the diagnosis becomes more complex when a patient self-medicates with rescue medications without initially characterizing the primary headache.[8] It is frequently associated with gastrointestinal symptoms, restless limbs, and asthenia.[9] Overuse of ergot has distinct characteristics including hemodynamic instability, paresthesia, arterial hypertension, dizziness, and limb weakness.[10]

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Complications

The most common rescue drugs are ergot derivatives causing adverse effects not limited to cognition defects, sensory neuropathies,[11] and disruption in cerebral vasculature. Intermittent claudication, acrocyanosis, rectal ulcers, persistent nausea, myocardial infarction, and fibrotic disorders are also reported. Although renal impairment is most vividly described for phenacetin-containing analgesics, most combination analgesics have a propensity to cause the same in acute or chronic forms.[12] Long-term use of triptans has been associated with ischemic colitis.[13]

Children and Adolescents

Combination drugs are often the culprits. Girls are more commonly (4:1) affected than boys.[14] Withdrawal therapy works better relatively in this age group compared to the adults with almost 53% responding in the form of a decrease in the number of headache days by 90%, regardless of preventive therapy.[15]

Prevention and Treatment

Healthcare authorities have a pivotal role to play regarding over-the-counter medications probably playing a huge role in increasing the prevalence of MOH especially in India where analgesics and proton pump inhibitors are prescribed at the drop of a hat. Consumption of tramadol in combination with paracetamol has trebled in the years between 2008 and 2015.[16]

The role of primary care physicians here is far more than the specialists in educating the patients regarding MOH, instructing them to keep a headache diary and referring patients to the specialists when needed. Headache campaigns and programs need to be formulated at the level of community. Such a campaign in Denmark, which reached a mere 10% of the population, resulted in significant awareness and reduction in MOH.[17] MOH of more than 2 years does not augur well in children and adolescents.[5]

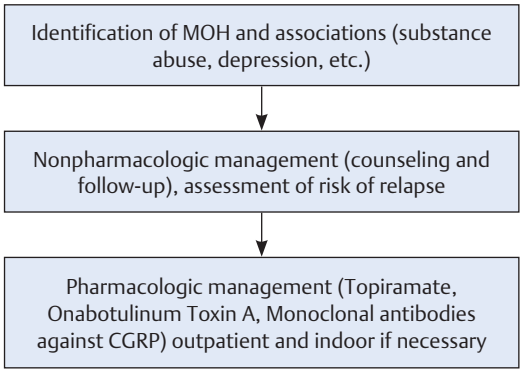
Identification of MOH and associations (substance abuse, depression, etc.)
Nonpharmacologic management (counseling and follow-up), assessment of risk of relapse
Pharmacologic management (Topiramate, Onabotulinum Toxin A, Monoclonal antibodies against CGRP) outpatient and indoor if necessary

Fig. 4.1 Proposed algorithm for management[18]

Treatment will comprise the following:

- Patient awareness.
- Prevention of primary headache using pharmacologic and nonpharmacologic means.
- Discontinuation of overused drugs.
- Legislation regarding over-the-counter availability of analgesics (**Fig 4.1**).

Goals of Detoxification

- Ceasing overused medication: The primary goal is to stop the overused medications, whether they are analgesics, triptans, ergotamines, or opioids.
- Reducing headache frequency: By stopping medication overuse, the aim is to decrease the frequency of headaches over time.
- Preventing relapse: Developing a long-term plan to manage headaches without falling back into overuse.

Methods of Detoxification

- Abrupt withdrawal:
  - Recommended for most medications like triptans or simple analgesics (e.g., ibuprofen, acetaminophen).

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  - Typically, the patient stops the overused medication all at once.
  - This can lead to an initial worsening of headaches (rebound headaches), which usually subsides in a few days to weeks.
- Gradual tapering:
  - Necessary for medications like opioids, barbiturates, or benzodiazepines, where sudden withdrawal can cause serious side effects.
  - The dose is reduced slowly over time to minimize withdrawal symptoms.
- Bridge therapy: During detoxification, certain medications (such as corticosteroids or non-overused preventive medications) may be temporarily used to help manage withdrawal symptoms and prevent rebound headaches.

Supportive Measures

- Preventive medications: Prophylactic treatments (e.g., beta-blockers, antiepileptics, or antidepressants) are often introduced before or during detox to help reduce the frequency of headaches once overuse is stopped.
- Hydration and nutrition: Proper hydration and nutrition can help the body recover during the detox process.
- Nonpharmacological therapies: Cognitive–behavioral therapy, biofeedback, and stress management techniques can support detox and prevent relapse.

Challenges

Rebound headaches: The initial worsening of headaches after stopping medication can be distressing for patients, making it important for healthcare providers to offer reassurance and support during this period.

Psychological dependence: Some patients may feel anxious or dependent on their medications, requiring psychological or behavioral support.

Long-Term Management

Once detoxification is complete, patients are often started on preventive treatments for their headaches and instructed on the careful, limited use of acute headache medications to avoid a return to MOH. Monitoring and follow-up are crucial to ensure adherence to treatment and prevent relapse. Detoxification for MOH should be tailored to the specific medication being overused, the patient's headache history, and any comorbidities that they may have.

Drug discontinuation causes withdrawal symptoms which again depend upon the offending drug, e.g., shorter duration for triptans than for ergotamine, NSAIDs, or opioids.[19] The withdrawal symptoms last hardly more than 2 weeks and are commonly found to be a worsening of pre-existing headache, sleep disorders, and anxiety.

Treatment of Withdrawal Headache

Withdrawal headaches, often experienced during the cessation of medications like caffeine, painkillers, or other drugs, can be challenging to manage. Although steroids, antipsychotics, sodium valproate, and tricyclic antidepressants have been suggested for treating withdrawal symptoms, placebo-controlled trials have not robustly confirmed their efficacy for withdrawal headaches.[20]

Steroids

Open-label studies are showing that prednisone can facilitate analgesic withdrawal by improving withdrawal symptoms, and these studies report very few adverse effects.[21] A small placebo-controlled trial also showed the benefits of oral prednisone in this context.

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However, subsequent studies failed to replicate the positive results seen in the initial trials.[22]

Antipsychotics

A retrospective, noncontrolled study[23] involving 135 chronic daily headache patients, many of whom also had MOH, suggested that intravenous prochlorperazine may be effective. However, since many patients were also taking other preventive medications, the drug's specific effectiveness could not be definitively determined.

Sodium Valproate

Intravenous valproate is used in patients with MOH to manage withdrawal headaches, typically when conventional treatments are insufficient. In this approach, the loading dose of 15 mg/kg over 30 minutes followed by maintenance doses of 5 mg/kg every 8 hours over 12 to 48 hours is aimed at reducing withdrawal symptoms.[24] Although this study demonstrated modest effectiveness, it highlights that valproate can be helpful in certain cases, even in acute settings. Moreover, valproate is also used orally for the long-term prevention of migraines, which aligns with its broader role in managing chronic migraine conditions, particularly in cases where patients do not respond to first-line treatments. Its oral use is more common in prophylactic therapy, depending on the patient's profile and specific needs. However, clinicians must consider the side effects and risk factors associated with valproate, particularly in pregnant women or individuals with liver conditions.

Follow-Up

- Drug monitoring and overuse:
  - Patients using symptomatic drugs not recommended for headache treatment (e.g., ergotamine, opioids, drug combinations) should be closely monitored.
  - NSAIDs rarely cause MOH, and managing triptan overuse is often simpler.
- Preventive treatments for migraine patients: Early preventive treatment is important, especially for migraine sufferers using drugs like:
  - Topiramate (an anticonvulsant).
  - OnabotA (OnabotulinumtoxinA or Botox).
  - Monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) ligand or receptor, known to be effective in preventing migraines.
- Nonpharmacological approaches: Behavioral therapy, stress-coping strategies, and regular exercise are mentioned as complementary methods to help manage MOH.
- Patient management and care: MOH patients should ideally be treated at specialized headache units. Although outpatient detoxification is preferred, hospitalization may be necessary in cases involving opioid or barbiturate overuse, recurrence, or certain comorbidities.

This comprehensive approach balances pharmacological and nonpharmacological treatments for better management of MOH.

Relapse rates can reach up to 50%, with most relapses occurring within the first year.[25] Several risk factors are identified including:

- A history of primary tension–type headaches.
- Extended periods of acute medication overuse before withdrawal.
- Use of a higher number of medications.
- Previous opioid use.[26]
- A history of substance use disorder, which may increase the risk of relapse.

This highlights the complexity of managing MOH and the importance of addressing these risk factors in treatment and follow-up plans.

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Conclusions and Future Directions

"An ounce of prevention is worth a pound of cure." Once MOH sets in, withdrawal of the overused drug is mandatory; otherwise, overuse will only be perpetuated and a vicious cycle ensues. Discontinuation of the overused medication is the stepping stone for the end of the menace. The modality of rescue needs to be individualized. The need of the hour is more properly designed randomized controlled trials for better evidence-based management.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders. 3rd ed. Cephalalgia 2018;38(1):1–211
2. Boes CJ, Capobianco DJ. Chronic migraine and medication-overuse headache through the ages. Cephalalgia 2005;25(5):378–390
3. Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. Headache 2006;46(Suppl 4):S202–S211
4. Westergaard ML, Hansen EH, Glümer C, Olesen J, Jensen RH. Definitions of medication-overuse headache in population-based studies and their implications on prevalence estimates: a systematic review. Cephalalgia 2014;34(6):409–425
5. González-Oria C, Belvís R, Cuadrado ML, et al. Documento de revisión y actualización de la cefalea por uso excesivo de medicación (CUEM). Neurologia (Engl Ed) 2021;36(3):229–240
6. De Felice M, Ossipov MH, Wang R, et al. Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain 2010;133(Pt 8):2475–2488
7. Munksgaard SB, Bendtsen L, Jensen RH. Modulation of central sensitisation by detoxification in MOH: results of a 12-month detoxification study. Cephalalgia 2013;33(7):444–453
8. Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol 2016;12(10):575–583
9. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA. Risk factors for medication-overuse headache: an 11-year follow-up study. The Nord-Trøndelag Health Studies. Pain 2012;153(1):56–61
10. Chen CL, Yeh YC, Chen YY. Ergotamine use and overuse in Taiwan: a retrospective cohort study. Headache 2018;58(3):416–423
11. Roon KI, Bakker D, van Poelgeest MI, van Buchem MA, Ferrari MD, Middelkoop HA. The influence of ergotamine abuse on psychological and cognitive functioning. Cephalalgia 2000;20(5):462–469
12. Barenbrock M, Spieker C, Witta J, et al. Reduced distensibility of the common carotid artery in patients treated with ergotamine. Hypertension 1996;28(1):115–119
13. Hodge JA, Hodge KD. Ischemic colitis related to sumatriptan overuse. J Am Board Fam Med 2010;23(1):124–127
14. Pakalnis A, Butz C, Splaingard D, Kring D, Fong J. Emotional problems and prevalence of medication overuse in pediatric chronic daily headache. J Child Neurol 2007;22(12):1356–1359
15. Kossoff EH, Mankad DN. Medication-overuse headache in children: is initial preventive therapy necessary? J Child Neurol 2006;21(1):45–48
16. Riederer F, Gantenbein AR, Marti M, Luechinger R, Kollias S, Sándor PS. Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: possible influence of orbitofrontal cortex. J Neurosci 2013;33(39):15343–15349
17. Carlsen LN, Westergaard ML, Bisgaard M, Schytz JB, Jensen RH. National awareness campaign to prevent medication-overuse headache in Denmark. Cephalalgia 2018;38(7):1316–1325
18. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol 2019;18(9):891–902
19. Leira Mui~no R, Dominguez C, Gómez Gallego M, Garrido Robres JA, Sanahuja J. Cefaleas secundarias (I). En: Guía oficial de práctica clínica en cefaleas. Guías diagnósticas y terapéuticas de la Sociedad Espa~nola de Neurología 2015. En: Ezpeleta D, Pozo-Rosich P, eds. Madrid: Luzan SA; 2015; 183–204
20. de Goffau MJ, Klaver ARE, Willemsen MG, Bindels PJE, Verhagen AP. The effectiveness of treatments for patients with medication overuse headache: a

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systematic review and meta-analysis. J Pain 2017; 18(6):615–627
21. Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. Cephalalgia 2003;23(10):982–993
22. Bøe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. Neurology 2007;69(1):26–31
23. Lu SR, Fuh JL, Juang KD, Wang SJ. Repetitive intravenous prochlorperazine treatment of patients with refractory chronic daily headache. Headache 2000;40(9):724–729
24. Schwartz TH, Karpitskiy VV, Sohn RS. Intravenous valproate sodium in the treatment of daily headache. Headache 2002;42(6):519–522
25. Chiang CC, Schwedt TJ, Wang SJ, Dodick DW. Treatment of medication-overuse headache: a systematic review. Cephalalgia 2016;36(4): 371–386
26. Vandenbussche N, Laterza D, Lisicki M, et al. Medication-overuse headache: a widely recognized entity amidst ongoing debate. J Headache Pain 2018;19(1):50

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5 Awake versus Asleep Mapping for Gliomas

Prakash Shetty, Vikas Singh, Parthiban Velayutham, and Aliasgar V. Moiyadi

Introduction

Surgical resection is a cornerstone in the treatment of gliomas, which are diffuse, infiltrative tumors that are challenging to excise completely. Greater extents of resection (EORs) have been associated with improved survival outcomes.[1–4] However, the risk of neurological morbidity escalates with increased resection. Preservation of neurological function is a critical predictor of survival, necessitating a careful balance between maximal tumor resection and functional preservation.

A variety of adjuncts are employed during surgery to enhance EOR while preserving neurological function. Intraoperative neuromonitoring (IONM) is a vital tool for safeguarding neurological function, particularly for tumors located near eloquent brain areas. A meta-analysis by De Witt Hamer et al involving 90 studies demonstrated that early neurological deficits were more common with IONM compared to no IONM (36% vs. 11.3%). However, these deficits often resolved during follow-up, resulting in lower long-term deficits (3.4% vs. 8.2%). Additionally, IONM was associated with higher EOR, particularly for tumors in eloquent areas.[5]

The choice between awake and asleep mapping in glioma surgery should be considered from two perspectives: understanding the functional localization within the brain and identifying the appropriate IONM techniques that can be utilized under either general anesthesia (GA) or awake conditions to preserve these functions.

Functional Localization in the Brain

Functional Localization in the Dominant and Nondominant Hemispheres

Functional localization in the brain can be divided into the dominant and nondominant hemispheres. The left hemisphere, dominant for most individuals, is primarily responsible for language processing, including comprehension of specific details, factual information, and the temporal sequencing of events. The right hemisphere is involved in the abstract and contextual aspects of language, such as emotion, tone, and prosody, as well as visuospatial processing. The functional localization of key neuropsychological domains is summarized in the **Table 5.1.** The right hemisphere's involvement in important functions is elaborated in a paper by Vilasboas et al.[6] For example, the right supplementary motor area (SMA) and premotor cortex, in addition to controlling the left limbs, coordinate bilateral limb movements in tasks requiring bimanual coordination.[7,8] Direct electrical stimulation (DES) of the right inferior fronto-occipital fasciculus (IFOF) can lead to left visual hemiagnosia, affecting visual recognition.[9] Stimulation of the supramarginal gyrus and superior longitudinal fasciculus (SLF) 2 may impair spatial cognition, resulting in a rightward deviation on line bisection tests.[10]

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Table 5.1 Localization of key neuropsychological domains in the cerebral hemispheres

	Left hemisphere	Right hemisphere
Language	Dominant for language (Broca's, Wernicke's)	Prosody, tone, contextual understanding
Visuospatial	Not primarily involved	Spatial orientation, facial recognition, constructional abilities
Attention	Selective and sustained attention	Vigilance and arousal
Memory	Verbal memory	Nonverbal and spatial memory
Executive function	Planning, reasoning, problem-solving	Emotional processing, social cognition
Emotion recognition	Less involved	Facial emotion recognition, empathy
Praxis	Ideomotor apraxia, verbal praxis	Visual and constructional praxis

In patients with right hemisphere language dominance, DES results mimic those in patients with left hemisphere dominance.[11]

Functional Anatomy of Gray (Cortical) and White (Subcortical) Matter

Traditionally, brain functions were thought to be localized to the cortical surface, but white matter tracts connecting these areas are equally significant. Understanding the functional anatomy of these structures aids in surgical planning, including the selection of anesthesia (awake or GA) and intraoperative testing of functions. The functional localization of cortical areas and subcortical tracts is summarized in **Table 5.2** and **Table 5.3**, respectively.

Neuropsychological Assessment

A thorough neuropsychological assessment is essential to identify baseline deficits in motor and higher cognitive functions. Basic screening tests like the mini-mental state examination (MMSE) can be used for initial evaluation, while more comprehensive batteries like the Addenbrooke's cognitive examination-III (ACE-III), Montreal cognitive assessment (MoCA), etc. offer detailed assessments of various neurocognitive domains.[12] The primary domains of neurocognition include:

- **Attention and arousal**: Essential for performing tasks in other domains. Attention refers to the ability to focus on a task despite the presence of distractions.
- **Language**: Encompasses expressive and receptive language, reading, and writing. Speech disorders include various types of aphasia, such as Broca's, Wernicke's, global, conduction, and transcortical.
- **Memory**: Includes immediate, short-term, long-term, episodic, semantic, and procedural memory.
- **Visuospatial ability**: The ability to interpret visual information and use spatial information for various tasks. Disorders can lead to neglect and some forms of apraxia, such as constructional apraxia.
- **Higher order functions**: Executive function relates to decision-making, planning, execution, and monitoring of goal-directed tasks. It also includes judgment, abstraction, learning, problem-solving, cognitive flexibility, and personality.
- **Social cognition**: Includes emotional recognition (facial emotional recognition, emotional prosody), empathy (the ability to feel and understand others' emotions), and theory of mind (ToM), which is the ability to understand others' thoughts, beliefs, and emotions.

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Table 5.2 Functional localization of cerebral cortex

Anatomical area	Left hemisphere (dominant)	Right hemisphere (nondominant)
Frontal lobe		
Dorsolateral prefrontal cortex	Working memory, planning, reasoning, problem-solving	Spatial awareness, visual–motor coordination
Dorsomedial prefrontal cortex	Intention to perform tasks, action initiation	Social cognition, decision-making in social contexts
Ventrolateral prefrontal cortex	Language processing (Broca's area)	Emotional regulation, response inhibition
Ventromedial prefrontal cortex	Decision-making, risk assessment	Emotional processing, social behavior
Supplementary motor area	Initiation and planning of complex movements	Coordination of bimanual movements
Temporal lobe		
Superior temporal gyrus	Auditory processing, language comprehension (Wernicke's)	Emotional tone of language, music perception
Inferior temporal gyrus	Visual object recognition	Visual object recognition, face processing
Middle temporal gyrus	Semantic memory, language processing	Spatial memory, visual navigation
Parietal lobe		
Superior parietal lobule	Sensory integration, spatial attention	Spatial orientation, body awareness
Inferior parietal lobule	Language, mathematical processing	Spatial awareness, visuospatial processing
Occipital lobe		
Primary visual cortex (V1)	Initial processing of visual information	Initial processing of visual information
Visual association areas	Interpretation of visual information	Interpretation of visual information
Insula		
Anterior insula	Emotional awareness, interoceptive awareness	Emotional awareness, empathy, and visceral functions
Posterior insula	Visceral sensory processing, taste perception	Visceral sensory processing, pain perception
Limbic lobe		
Cingulate cortex	Emotion formation, cognitive control, learning, memory	Emotional processing, decision-making, empathy
Parahippocampal gyrus	Memory encoding and retrieval	Spatial memory, navigation

Other motor and sensory higher functions include:

- **Apraxia**: The inability to perform a learned, purposeful motor task despite an intact motor system. Apraxia can be ideational (lack of memory to perform a task) or ideomotor (difficulty in executing the task). Some features may overlap with deficits in executive function.
- **Agnosia**: A perceptual disorder characterized by the inability to recognize objects, persons, sounds, shapes, or smells despite having the physical ability to see, smell, and hear. Agnosia can lead to various neglect disorders.

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Table 5.3 Functional anatomy of major white matter tracts

Tracts	Left hemisphere	Right hemisphere
SLF 1	Connects parietal to frontal lobe; involved in attention, executive function	Contributes to visuospatial processing
SLF 2	Links parietal lobe with frontal; supports working memory, language	Involved in spatial awareness, attention
SLF 3	Connects inferior parietal lobule with frontal lobe; involved in language processing	Similar role in spatial perception and motor planning
Arcuate fasciculus	Connects frontal to temporal–parietal region; critical for language	May assist in audio-visuospatial orientation
Frontal aslant tract	Connects SMA to inferior frontal gyrus, involved in speech initiation	Nonverbal planning, motor planning
IFOF	Connects frontal to occipital lobes; crucial for semantic processing and reading	Contributes to visual recognition, spatial processing
Uncinate fasciculus	Links frontal and temporal lobes; involved in emotion regulation, social cognition	Similar function in processing emotional and social cues
Middle longitudinal fasciculus	Connects temporal and parietal lobes; auditory processing, language comprehension	Supports similar functions in auditory processing
Inferior longitudinal fasciculus	Connects occipital to temporal lobes; visual memory and object recognition	Involved in face and scene recognition, visual processing

Abbreviations: IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; SMA, supplementary motor area.

Preoperative Imaging

MRI of brain (tumor protocol) is required to assess the grade, location, and morphology of the tumor. In addition, specialized imaging sequences like tractography and functional MRI may be needed depending on the location of the lesion. In patients who are not cooperative for a task based functional MRI, a resting state MRI of brain can be performed to assess the functional areas. The finding of the functional MRI serves as a guide; however, discrepancies may occur with intraoperative findings, especially for speech function, where sensitivity was reported from 59 to 100%.[13] Sometimes patients may be denied appropriate surgery based on presumed eloquence on preoperative MRI.[14]

Preoperative Assessment

The choice of surgical approach for glioma patients depends on various factors, including patient-related factors, tumor-related factors, and environmental factors. Awake surgery is required for mapping of higher level functions in tumors close to these functional pathways; however, not everybody is a candidate to undergo awake surgery. Contraindications to awake surgery include extremes of age, obesity with airway obstruction, difficult airway, severe neurological deficits, uncontrolled seizures, anxiety, and psychiatric disorders. Tumor-related factors include a high-grade tumor with midline shift (relative contraindication). Also, environmental factors include availability of expertise and

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equipment etc. GA is considered as an option in these patients. Also, GA is considered for non-eloquent tumor, but the definition of non-eloquent is rapidly changing. Areas previously thought to be non-eloquent such as like right frontal lobe are operated under awake conditions for higher function preservation.

Role of Intraoperative Neuromonitoring (IONM)

IONM Techniques

Awake or asleep surgery is determined by the functions to be monitored. Basic motor (motor evoked potential [MEP], D-wave), sensory (somatosensory evoked potential [SSEP]), auditory (brainstem auditory evoked potential [BAER]), vision (visual evoked potential [VEP]), and cranial nerve monitoring can be performed under GA. However, higher-order functions that require input from supplementary and association areas cannot be monitored under GA. These functions include complex/fine motor tasks, language, memory, visuospatial skills, social cognition (including emotions), and executive functions.[15] These are summarized in **Table 5.4**. Traditionally, only left hemispheric functions such as speech were monitored under awake conditions, but there is an increasing trend toward monitoring right hemispheric functions as well.

Various types of mapping and monitoring techniques are utilized in IONM. Mapping refers to techniques that assess the integrity of neural pathways from the point of stimulation to the peripheral effector organs at a specific point in time. Monitoring involves repetitive evaluation of the entire neural pathway through electrical stimulation or clinical assessment. Ideally, a combination of mapping and monitoring techniques is used during surgery. The two common stimulation parameters used are low frequency (50–60 Hz) (LF) and high frequency (250 Hz) (HF). LF stimulation is typically used under awake conditions, while HF stimulation is used under GA. Reverse combinations is possible, but less commonly employed due to certain limitations.

Table 5.4 Selection of IONM techniques and anesthesia for function preservation

	General anesthesia	Awake
Functions monitored	Motor, sensory, vision, auditory, cranial nerves (motor)	Motor/complex motor, language, executive functions, visuospatial functions, social cognition, vision
Stimulation technique (common)	High frequency (250 Hz) monopolar	Low frequency (50–60 Hz) bipolar
Stimulation technique (rare)	Low frequency with modifications	High frequency with modification
IONM type	Mapping, monitoring	Mapping, monitoring
	Cortical motor mapping, subcortical motor mapping, cranial nerve mapping	Active functional mapping with electrical stimulation and clinical response assessment
	Motor evoked potentials (MEP), SSEP, VEP, BAER, and reflex arc monitoring	Passive clinical monitoring without stimulation

Abbreviations: BAER, brainstem auditory evoked potential; IONM, intraoperative neuromonitoring; SSEP, somatosensory evoked potential; VEP, visual evoked potential.

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Practical Considerations for Awake vs. Asleep Surgery Depending on Function to be Preserved

Motor Function (GA or Awake)

The original Penfield technique: Use of LF stimulation (50–60 Hz) to monitor motor functions in awake patients was described in 1937. A modification of this technique for motor mapping under GA was described in 1991 by LeRoux et al, but it requires higher currents and carries a higher risk of inducing seizures.[16] In the late 1990s, Taniguchi et al developed an HF stimulation technique (250 Hz) that enabled the recording of MEPs under GA.[17]

A study by Kombos et al comparing LF (50 Hz) and HF (250 Hz) stimulation found that both HF monopolar and LF bipolar stimulation were equally effective for mapping the primary motor cortex. However, HF monopolar was preferred because of its mapping and continuous monitoring ability. In the premotor frontal cortex, bipolar LF stimulation was more sensitive for localizing functions than monopolar HF stimulation.[18] Therefore, a combination of bipolar mapping and monopolar monitoring is preferred for tumors in the SMA region (praxis network). Bipolar stimulation of motor cortex in awake patients results in motor movement, while stimulation of the SMA can result in negative motor phenomena (delay, distortion, or inhibition of planned movements).[19] HF stimulation of the motor cortex can elicit muscle MEPs without noticeable muscle movement.

For lesions around the central sulcus, HF stimulation under GA is used to preserve motor pathways especially in patients with deficits and recurrent disease.[20] Subcortical motor pathways can be continuously mapped using a suction stimulator with HF stimulation, which was devised by Andreas Raabe and colleagues.[21] This technique ensures the safety of the corticospinal tract (CST) during subcortical resection by establishing a current–distance relationship (1 mA = 1 mm distance from the CST).

For tumors involving the SMA and pre-SMA regions, there is debate over the preferred IONM technique. Some advocate for HF stimulation under GA, which results in temporary weakness that typically recovers with minimal residual deficits and increased gross total resection (GTR) rates.[22] Others prefer awake surgery with bipolar LF stimulation to map the SMA and resect the tumor based on stimulation findings, preserving neurological function, including fine motor tasks and bimanual coordination, though this may necessitate leaving tumor tissue in place if it involves functional areas. Nakajima et al described motor events like slowing, delay in initiation, and coordination disturbance in the absence of positive mapping during awake surgery, which could predict a reversible SMA syndrome.[23]

Motor tasks during awake surgery include handgrip tasks, finger tapping, and limb movement upon command.

Language Function (Awake)

Language mapping is only possible under awake conditions using bipolar LF stimulation. Verbal language functions are typically localized in the dominant hemisphere (left) around the perisylvian area. The key tracts associated with speech function include the arcuate fasciculus, SLF 3, and IFOF. Intraoperative tests such as picture naming or verb generation are used to map language pathways, with bipolar LF stimulation applied for 3 to 5 seconds before administering the test. Speech errors such as anomia, perseveration, paraphasia, dysarthria, and speech arrest (without tongue twitching) may occur during stimulation. Continuous speech monitoring is conducted throughout the surgery. Similar findings can occur in patients with right hemisphere lesions who are left-handed or ambidextrous or who have preoperative speech disturbances. Monitoring of nonverbal semantics (IFOF) is performed for right

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hemisphere lesions. Other language tests include reading, repetition, fluency testing (phonemic/semantic), action naming, and diadochokinetic task.

Visuospatial Function (Awake)

Visuospatial function is predominantly localized in the right hemisphere and cortical areas involved include the temporoparietal junction and ventral frontal cortex. Some studies have implicated SLF 3 in the subcortical pathways, while others have suggested the involvement of SLF 2.[24] The most commonly employed intraoperative test for visuospatial function in awake patients is line bisection, with deviation to the right side on stimulation of these areas by bipolar LF stimulation. However, some studies have shown that patients with unilateral neglect (UN) may still perform normally on a line bisection test. Other tests used intraoperatively include the target cancellation test and clock face drawing.[25,26]

Social Cognition (Awake)

Social cognition is a complex function involved in social interaction, including emotional recognition, empathy, and ToM. Ekman's test or the "Mind in the Eyes" test can be used to assess facial emotion recognition intraoperatively in awake patients using bipolar LF stimulation. The right superior temporal gyrus, middle temporal gyrus, and left insula have been associated with facial emotion recognition. Empathy and ToM involve distinct but overlapping networks, including the prefrontal cortex (PFC), orbitofrontal cortex (OFC), supramarginal gyrus (SMG), angular gyrus (AG), left middle temporal gyrus (MTG), and uncinate fasciculus.[27]

Attention and Working Memory (Awake)

Attention and working memory are tested intraoperatively using forward and backward digit span tasks.

Memory Function Monitoring (Awake)

Memory is assessed intraoperatively by word list recall and object recognition tasks.

Executive Function Monitoring (Awake)

Executive function is a higher-order cognitive function that requires both hemispheres for goal-directed activities involving planning, execution, and monitoring. It is tested intraoperatively using task-switching, dual-task paradigms, or a Stroop test using bipolar LF stimulation.

Recent systematic review showed that language testing continues to be the most commonly tested domain during awake surgery; however, there is trend toward increased testing in domains like monitoring visuospatial functions, social cognition, and executive functions.[28]

Summary

In glioma surgery, achieving a balance between maximal tumor resection and the preservation of neurological function is paramount. The EOR is closely linked to improved survival outcomes, yet it carries the inherent risk of increased neurological morbidity. IONM plays a crucial role in mitigating these risks, particularly for tumors near eloquent brain areas. The decision between awake and asleep surgery should be guided by a detailed understanding of functional brain localization and the specific IONM techniques suitable for preserving critical functions. Although awake surgery is essential for mapping higher-order cognitive functions, GA with appropriate IONM may be more suitable in cases where awake surgery is contraindicated. The integration of functional and anatomical brain mapping with neuropsychological assessment and advanced imaging techniques ensures a tailored surgical approach that maximizes resection while preserving vital neurological functions.

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References

1. Aghi MK, Nahed BV, Sloan AE, Ryken TC, Kalkanis SN, Olson JJ. The role of surgery in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2015;125(3): 503–530
2. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26(8):1338–1345
3. Wijnenga MMJ, French PJ, Dubbink HJ, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. Neuro-oncol 2018;20(1): 103–112
4. Hervey-Jumper SL, Zhang Y, Phillips JJ, et al. Interactive effects of molecular, therapeutic, and patient factors on outcome of diffuse low-grade glioma. J Clin Oncol 2023;41(11):2029–2042
5. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 2012; 30(20):2559–2565
6. Vilasboas T, Herbet G, Duffau H. Challenging the myth of right nondominant hemisphere: lessons from corticosubcortical stimulation mapping in awake surgery and surgical implications. World Neurosurg 2017;103:449–456
7. Rech F, Herbet G, Moritz-Gasser S, Duffau H. Disruption of bimanual movement by unilateral subcortical electrostimulation. Hum Brain Mapp 2014;35(7):3439–3445
8. Kinoshita M, de Champfleur NM, Deverdun J, Moritz-Gasser S, Herbet G, Duffau H. Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal mapping study. Brain Struct Funct 2015;220(6):3399–3412
9. Fernández Coello A, Duvaux S, De Benedictis A, Matsuda R, Duffau H. Involvement of the right inferior longitudinal fascicle in visual hemiagnosia: a brain stimulation mapping study. J Neurosurg 2013;118(1):202–205
10. Vallar G, Bello L, Bricolo E, et al. Cerebral correlates of visuospatial neglect: a direct cerebral stimulation study. Hum Brain Mapp 2014;35(4):1334–1350
11. Duffau H, Leroy M, Gatignol P. Cortico-subcortical organization of language networks in the right hemisphere: an electrostimulation study in left-handers. Neuropsychologia 2008;46(14): 3197–3209
12. Larner AJ, ed. Cognitive Screening Instruments. Springer; 2016
13. Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. Neurosurgery 2010;66(1):113–120
14. Duffau H. The challenge to remove diffuse low-grade gliomas while preserving brain functions. Acta Neurochir (Wien) 2012;154(4):569–574
15. Szelényi A, Bello L, Duffau H, et al; Workgroup for Intraoperative Management in Low-Grade Glioma Surgery within the European Low-Grade Glioma Network. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus 2010;28(2):E7
16. LeRoux PD, Berger MS, Haglund MM, Pilcher WH, Ojemann GA. Resection of intrinsic tumors from nondominant face motor cortex using stimulation mapping: report of two cases. Surg Neurol 1991; 36(1):44–48
17. Taniguchi M, Cedzich C, Schramm J. Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. Neurosurgery 1993;32(2):219–226
18. Kombos T, Suess O, Kern BC, et al. Comparison between monopolar and bipolar electrical stimulation of the motor cortex. Acta Neurochir (Wien) 1999;141(12):1295–1301
19. Lüders HO, Dinner DS, Morris HH, Wyllie E, Comair YG. Cortical electrical stimulation in humans. The negative motor areas. Adv Neurol 1995;67:115–129
20. Rossi M, Puglisi G, Conti Nibali M, et al. Asleep or awake motor mapping for resection of perirolandic glioma in the nondominant hemisphere? Development and validation of a multimodal score to tailor the surgical strategy. J Neurosurg 2021;136(1):16–29
21. Raabe A, Beck J, Schucht P, Seidel K. Continuous dynamic mapping of the corticospinal tract during surgery of motor eloquent brain tumors: evaluation of a new method. J Neurosurg 2014;120(5):1015–1024
22. Kumar G K, Chigurupalli C, Balasubramaniam A, Rajesh BJ, Manohar N. Role of asleep surgery

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for supplementary motor area tumors. Indian J Neurosurg 2023;12(2):132–136

23. Nakajima R, Nakada M, Miyashita K, et al. Intraoperative motor symptoms during brain tumor resection in the supplementary motor area (SMA) without positive mapping during awake surgery. Neurol Med Chir (Tokyo) 2015;55(5):442–450
24. Bernard F, Lemée JM, Ter Minassian A, Menei P. Right hemisphere cognitive functions: from clinical and anatomic bases to brain mapping during awake craniotomy. Part I: clinical and functional anatomy. World Neurosurg 2018;118:348–359
25. Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature. 2001 Jun 21; 411(6840):950-953.
26. Binder J, Marshall R, Lazar R, Benjamin J, Mohr JP. Distinct syndromes of hemineglect. Arch Neurol. 1992 Nov;49(11):1187-1194.
27. Lemée JM, Bernard F, Ter Minassian A, Menei P. Right hemisphere cognitive functions: from clinical and anatomical bases to brain mapping during awake craniotomy. Part II: neuropsychological tasks and brain mapping. World Neurosurg 2018; 118:360–367
28. de Zwart B, Ruis C. An update on tests used for intraoperative monitoring of cognition during awake craniotomy. Acta Neurochir (Wien) 2024; 166(1):204

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6 Programmable Shunts for Infantile Hydrocephalus: A Controversial Choice or a Scientific Paradox?

Suhas Udayakumaran

Introduction

It has long been known that treating younger children with hydrocephalus presents challenges. The foundation of contemporary cerebrospinal fluid (CSF) diversion continues to be ventriculoperitoneal shunting and differential pressure valves to make it possible. The availability and variety of valve designs have grown exponentially, but there has yet to be much in-depth comparison. Selecting a shunt valve is a contentious issue in neurosurgery, not just in pediatrics. The lack of randomized trial data has made it challenging to compare valve designs objectively. New research indicates there might not be any design that is more effective than any other in the newborn and infant population.[1]

This chapter will review the current state of the art in valve selection and the controversies surrounding neonates and infants. This controversial subject does not include the loculated forms of hydrocephalus-like arachnoid cysts.

Hydrocephalus and normal intracranial pressure (ICP) in prematurity, neonates, and infants—*do we understand enough of the complex pathophysiology?*

Germinal matrix hemorrhage is commonly associated with prematurity. A subgroup of newborns weighing less than 1500 g at delivery will develop post-hemorrhagic hydrocephalus (PHH), which requires surgical intervention. Between 15 and 20% of infants will develop intraventricular hemorrhage (IVH), despite advancements in perinatal care appearing to reduce the incidence.[1–3] Historically, poor results, including high rates of infection and shunt failure, have been linked to the early implantation of definitive CSF diversion techniques in PHH, such as ventriculoperitoneal (VP) or ventriculoatrial (VA) shunts.[2–5] There is support for initiating early diversion of CSF[6] but understanding or precisely diagnosing hydrocephalus and the need for diversion is challenging.[5,7] Unlike for PHH and occasionally post-infective hydrocephalus, for congenital etiologies, the decision-making and timing may be more definite.

"Normal" ICP in Neonates and Infants

ICP is an essential aspect of normal brain function and homeostasis. However, there is little evidence for normal ICP values in children, and normative values do not exist for ICP in neonates and infants.

Establishing normal ICP values in neonates and infants is particularly challenging due to ethical and practical limitations. Noninvasive methods for ICP estimation are improving but still lack the accuracy required for continuous daily monitoring. Determining the normal

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reference range for ICP in healthy children necessitates a cohort with no suspicion of CSF pathology. As a result, reference values for normal ICP in children are frequently extrapolated from adult data or derived from pediatric patients with suspected abnormal ICP, which are straightforward pseudonormal patient populations, such as those without evident ICP or CSF pathology.

In addition to these challenges, measured ICP is often greater than the calculated value due to a vascular component. This discrepancy is likely the result of arterial pulsations and the interactions between pulsatile arterial inflow and venous outflow curves, cardiac function, and cerebral vasomotor tone.[4] Therefore, understanding and establishing normal ICP values in neonates and infants require careful consideration of these dynamic and interrelated factors.

ICP monitoring in pediatric patients can be challenging due to the variability in normal values based on the age, developmental stage, and underlying medical condition. For instance, studies have shown variations in normal ICP values across different pediatric age groups, ranging from infants aged 0 to 24 months to children up to 17 years old, reflecting the complexity of standardizing these measurements. Normal ICP values for neonates and infants generally range between 3 and 6 mmHg, with values up to 10 mmHg considered within the normal range under specific conditions. Managing elevated ICP in infants aims to maintain adequate cerebral perfusion pressure (CPP), which is essential for brain health, with normal CPP values in young children generally being lower than those in older children and adults.

Shunting has been a key game changer for managing hydrocephalus in all ages and improving cognitive outcomes.[8] Valves are key components of the implant used. Currently, options are fixed pressure and programmable shunts, with the recent generation of valves having additional mechanisms to negate gravity.[9,10] Thus, the diagnosis and timing of a permanent implant–based diversion are controversial. Added to this conundrum is the extent or target parameters for an optimal diversion for optimal cognitive development.[1,9,11,12] Diversion with a fixed-pressure valve in such a scenario is counter-intuitive, especially in the most crucial period in brain and cognitive development.[8,9,11]

How do we consistently place a permanent implant in infants if we do not understand the ICP and physiology of a normal brain in infants?

Controversies in Shunt Selection in Neonates and Infants: The Ideal First Shunt

A more comprehensive examination of shunt valve utilization in the preterm newborn population is required due to their unique complications, such as their higher risk of infection, loculated hydrocephalus, and slit ventricle syndrome.

If hydrocephalus is present and diversion is merited, using a programmable valve will allow us to tailor to the requirement based on the head circumference nomograms, especially when the ventricle may not be a good indicator, which is nearly well-studied.[7,13]

Best Shunt in Infants: Metrics of Decision-Making

There is an apparent lack of literature on significant cohort and prospective studies in this contentious area of decision-making in infantile hydrocephalus.[12,14] Reduced study power may have obscured results, as most studies could not find differences in shunt failure or complication rates for each type of valve. The metrics to compare shunts are obvious. They are:

- Complications.
- Shunt survival.
- Neurocognitive outcome.

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Avoidance of Shunt Complications

Although CSF overdrainage is treatable with programmable valves, little is known about the associated "slit ventricle" syndrome and craniocerebral disproportion, and how valve selection affects them. The long-term effects on the infant population are most likely greatest when subtle changes to ventricular morphology occur.

In children treated as infants, overdrainage symptoms can vary widely but often include headaches, nausea, vomiting, blurred vision, and dizziness. These symptoms may not manifest until later in childhood, although physiological changes within the brain can occur sooner. Symptoms, including postural or chronic headaches, as well as treatment for overdrainage, can significantly affect the quality of life (QoL).[15,16] Overdrainage can be prevented with anti-siphon or gravitational devices.[9,17]

Optimizing the first shunt implantation is of utmost importance. Recent work suggests that infants may experience overdrainage from unprotected differential pressure valves; however, low-pressure gravitational unit valves can stop overdrainage in up to age 5, and medium-pressure GU valves can allow physiological ICP to continue for at least 10 years. Consequently, the first implanted shunt should have overdrainage prevention mechanisms, and the opening pressure should be changed as the child grows,[9,10] thus making a programmable valve a choice.

These systems are usually more expensive than simple differential pressure valves, which may limit their use in low- and middle-income countries (LMICs).

Shunt Survival

Although the overall survival rates of patients with fixed and programmable pressure shunt valves are not statistically significant different, programmable valves require fewer changes for each patient in some circumstances. As such, they continue to play a vital part in treating this complicated patient population.[1]

Neurocognitive Outcome—Understanding the Current Literature and Its Limitations

No systematic data describe the behavior and variations in shunt drainage in a developing child throughout timelines. Many studies have examined the effectiveness of valves in treating acute hydrocephalus, but their role in averting developmental and neurocognitive deficits still needs to be improved.[9,17] However, programmable shunts are associated with better physical and cognitive outcomes than fixed-pressure shunts, improving health-related quality of life (HRQOL) in children with infantile hydrocephalus.

Role of Programmable Valve/Shunt in Shunt Independence

As infants grow, they may reduce their requirement for diversions, especially when inserted in post-hemorrhagic and post-infective hydrocephalus.[18]

According to Iannelli and colleagues, post-hemorrhagic hydrocephalus was the initial reason for shunt insertion in 41% of patients who went on to achieve shunt independence. Moreover, 88.9% had shunt insertions performed at birth, and many of them were born before term. They deduced from this that young patients with post-hemorrhagic hydrocephalus would experience a delayed maturity of their CSF dynamics, perhaps facilitating the gradual development of shunt independence.[18] A "minor pathway" may be more critical in allowing transependymal, perivascular, interstitial, and perineural lymphatic absorption of CSF into the venous system in the developing brain than the traditional mode of CSF absorption into the superior sagittal sinus via arachnoid granulations.[19] Patients who had shunts placed very early

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in life may gain shunt independence due to a mature balance of CSF absorptive mechanisms, which would coincide with the later physiological development of the more classically defined "major pathway."

One may consider the logic that the best way to minimize long-term shunt complications is to no longer need the shunt. This is feasible, especially in the presence of a programmable valve, by gradually escalating the resistive setting. This includes considering using ETV in older children with feasible anatomy and other factors, although failure must be anticipated. The programmable shunt allows a surrogate understanding of the physiology without changing with setting escalation, including the on–off option in some recent shunts (CERTAS™ Plus Programmable Valve, Integra LifeSciences, NJ, US), hence allowing for checking for shunt independence.

Pragmatic Application in Indian Scenario: A Commentary

Given that the survival rates of programmable and nonprogrammable valves are similar across all available data, it is unclear or rather contentious why the former, frequently more expensive, programmable valves, should be chosen.[11,20]

Although there is yet to be a clear outcome and complication data, considering the challenge of getting such specific data in a treatment scenario like ours,[20] with evidence that improved HRQOL may be associated with programmable valves, why the benefit should not be offered to all eligible infants?

An Open Question with an Improbable Solution: A Scientific Paradox

Some studies suggest programmable shunts for infantile hydrocephalus are safe, reduce complications, and improve outcomes. In contrast, other studies indicate no significant reduction in failure rates or revisions compared to nonprogrammable valves. Eventually, carefully planned multicenter trials will yield data that neurosurgeons can use to advise their youngest, most susceptible patients on the best ways to reduce postoperative complications, avoid permanent shunt dependency, and, most importantly, advance long-term neurodevelopmental outcomes.

Will we have clear objective answers for the complex question of diverse cognitive outcomes in infant hydrocephalus and its comparative treatment outcomes with various valves?

Conclusion

The literature lacks direct comparisons between valves, making it challenging to draw definitive conclusions about the superiority of fixed valves over programmable valves in infants. Additionally, the complexities and ambiguities surrounding normal ICP physiology in this age group question the appropriateness of using fixed-pressure valves during critical brain and cognitive development.

References

1. Hall BJ, Gillespie CS, Sunderland GJ, et al. Infant hydrocephalus: what valve first? Childs Nerv Syst 2021;37(11):3485–3495
2. Bock HC, Feldmann J, Ludwig HC. Early surgical management and long-term surgical outcome for intraventricular hemorrhage-related posthemorrhagic hydrocephalus in shunt-treated premature infants. J Neurosurg Pediatr 2018;22(1):61–67
3. Mazzola CA, Choudhri AF, Auguste KI, et al; Pediatric Hydrocephalus Systematic Review and Evidence-Based Guidelines Task Force. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: Management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 2014;14(Suppl 1):8–23
4. Ballabh P, de Vries LS. White matter injury in infants with intraventricular haemorrhage: mechanisms and therapies. Nat Rev Neurol 2021;17(4):199–214

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5. Cabacungan E, Adams S, Best B, Foy AB, Singh A, Cohen SS. Variability in neurosurgical management and associated comorbidities and complications among preterm patients with posthemorrhagic hydrocephalus in the United States. J Neurosurg Pediatr 2023:1–8. (e-pub ahead of print)
6. Chiarelli PA, Chapman N, Flyer BE, Chu JK, Krieger MD. Shunt timing in low-weight infants in the treatment of hydrocephalus. J Neurosurg Pediatr 2024;33(6):564–573
7. Paturu M, Triplett RL, Thukral S, et al. Does ventricle size contribute to cognitive outcomes in posthemorrhagic hydrocephalus? Role of early definitive intervention. J Neurosurg Pediatr 2021; 29(1):10–20
8. Kahle KT, Kulkarni AV, Limbrick DD Jr, Warf BC. Hydrocephalus in children. Lancet 2016; 387(10020):788–799
9. Bock HC, von Philipp G, Ludwig HC. An adjustable gravitational valve for initial VP-shunt treatment in hydrocephalic preterm neonates and infants below 1 year of age. Childs Nerv Syst 2021;37(11): 3497–3507
10. Zhang RS, Wes AM, Naran S, et al. Posterior vault distraction osteogenesis in nonsyndromic patients: an evaluation of indications and safety. J Craniofac Surg 2018;29(3):566–571
11. Fernández Cornejo VJ, Elbabaa SK. Shunt technology for infants and a lifetime. Childs Nerv Syst 2021;37(11):3475–3484
12. Robinson S, Kaufman BA, Park TS. Outcome analysis of initial neonatal shunts: does the valve make a difference? Pediatr Neurosurg 2002;37(6): 287–294
13. Cheong JL, Hunt RW, Anderson PJ, et al. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics 2008;121(6):e1534–e1540
14. Hall BJ, Ali AMS, Hennigan D, Pettorini B. Hydrocephalus in prematurity: does valve choice make a difference? Childs Nerv Syst 2024; 40(4): 1091–1098
15. Czosnyka Z, Czosnyka M, Copeman J, Pickard JD. A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Neurosurgery 2000;47(5): 1250–1251
16. Pollack IF, Albright AL, Adelson PD; Hakim-Medos Investigator Group. A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Neurosurgery 1999;45(6):1399–1408, discussion 1408–1411
17. Gebert AF, Schulz M, Schwarz K, Thomale UW. Long-term survival rates of gravity-assisted, adjustable differential pressure valves in infants with hydrocephalus. J Neurosurg Pediatr 2016; 17(5):544–551
18. Iannelli A, Rea G, Di Rocco C. CSF shunt removal in children with hydrocephalus. Acta Neurochir (Wien) 2005;147(5):503–507, discussion 507
19. Oi S, Di Rocco C. Proposal of "evolution theory in cerebrospinal fluid dynamics" and minor pathway hydrocephalus in developing immature brain. Childs Nerv Syst 2006;22(7):662–669
20. Zemack G, Romner B. Do adjustable shunt valves pressure our budget? A retrospective analysis of 541 implanted Codman Hakim programmable valves. Br J Neurosurg 2001;15(3):221–227

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7 Molecular Profiling for Brain Tumors—A Necessity or Luxury?

Vani Santosh and Shilpa Rao

Introduction

The classification of tumors of the central nervous system (CNS) is evolving rapidly. Although tumors were historically classified on the basis of morphology, the recent integration of molecular information has immensely refined this process. Starting with the earliest Bailey and Cushing[1] classification of 1926, and subsequently in the first four editions of the WHO classification of CNS tumors (1979–2007), the diagnosis, classification, and grading of CNS tumors have been based solely on histology, supplemented by basic immunohistochemistry (IHC) in the latter editions. Over the past two decades, understanding of the molecular alterations that impact tumor biology and treatment response has refined the classification significantly. These molecular alterations have an edge over morphology and currently form the basis for the diagnosis, classification, and prognosis of several brain tumors. A paradigm shift was observed in the revised 4th edition, i.e., the WHO 2016 classification, which incorporated morphologic and molecular information for the first time into the classification. Following this classification, there has been further advancements in the molecular pathology of CNS tumors, and in order to keep in pace with this, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT NOW) was established to advance recommendations on CNS tumor diagnosis between WHO editions.[1] Seven guideline papers have been published and the recommendations are largely adopted by the WHO 2021 classification, i.e., WHO CNS5.[2–8] As a result, the WHO CNS5 further advances the role of molecular diagnostics in CNS tumor classification, thereby reducing the dependency on morphologic features for tumor classification.

Is Molecular Testing Required for All Brain Tumors?

Molecular data has brought in a fundamental transition in the diagnosis and management of patients with several types of brain tumors, particularly the adult-type and pediatric-type gliomas, embryonal tumors, and very soon, tumors such as pituitary adenoma/pituitary neuroendocrine tumor (PitNET) and meningiomas will also see this change. In the WHO CNS5, molecular parameters have become an essential diagnostic criterion for providing a histomolecular diagnosis for certain CNS tumors. However, molecular parameters are not required for the characterization of all groups of tumors. There are some tumors that are grouped based on genetic changes that enable a complete diagnosis (examples: astrocytoma, IDH-mutant, and diffuse midline glioma, H3K27-altered). However, there are other tumors that can be diagnosed based only on histological features (examples: pilocytic astrocytoma and meningioma). For some, molecular parameters support the diagnosis but are not mandatory for the same (example: MAPK alterations in pediatric-type low-grade gliomas). For a few tumors, molecular features help define new tumor types and subtypes (example: medulloblastoma, WNT-activated or SHH-activated). Therefore, although molecular testing becomes mandatory to establish the diagnosis in some tumor types, it is not required for all the CNS tumors.

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In routine practice, first the patient's demographic data and the histological features of the tumor are considered. Approach to molecular testing can be in a stepwise manner. The initial histologic evaluation plays a crucial role in determining subsequent molecular workup. The pathologist formulates a list of differential diagnosis based on histology and then selects the appropriate molecular test. Analysis begins with immunohistochemistry (IHC) using diagnostic and surrogate molecular markers followed by simpler molecular techniques such as fluorescence in situ hybridization (FISH), DNA sequencing (Sanger), and polymerase chain reaction (PCR). This approach is beneficial and cost effective since the pathologist gets to select the most optimal test(s). In fact, there are several tumors where an integrated histomolecular diagnosis can be provided using IHC markers alone such as astrocytoma, IDH-mutant, and posterior fossa group A ependymoma. An alternative method consists of using techniques which allow for the detection of several molecular alterations using a single method such as the next generation sequencing (NGS) that includes targeted panel sequencing and/or whole exome/genome sequencing (WES/WGS). In recent years, DNA methylation profiling has become the most impactful tool for the accurate diagnosis and classification of brain tumors.[9] The technique is based on the epigenomic methylation signatures that can differentiate and help classify brain tumors. In addition, it provides valuable information on the copy number variations (CNVs) of an individual tumor which further confirms the diagnosis. However, the limitation of these high throughput tests is that they are not accessible in all the centers and are not cost effective and hence as of now NGS and methylation profiling are being employed for diagnostically challenging neoplasms or rare tumors. Furthermore, it is important to remember that NGS and methylation profiling platforms are generally employed when histology and workup with complete IHC panels and other molecular tests have already been carried out but still the case remains unresolved.[10] This further increases the cost and cannot be afforded by several patients.

This chapter briefly discusses the approach to some of the commonly occurring brain tumors where molecular testing can be optional or mandatory.

Adult-Type Diffuse Gliomas

Adult-type diffuse gliomas comprise three tumor types that are molecularly defined: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma (GBM), IDH-wild type.[11] Molecular testing is required for the diagnosis of these tumors to conform to the WHO CNS5 guidelines for diagnosis. The key molecular alterations in IDH-mutant astrocytomas include mutations of *IDH1* or *IDH2*, *ATRX*, and *Tp53* genes. These tumors do not harbor 1p/19 codeletion. They are graded as CNS WHO grades 2, 3, and 4. Oligodendrogliomas are characterized by IDH mutations and 1p/19q codeletion and are graded as CNS WHO grade 2 or 3. GBM is defined by IDH wild type status, corresponds to CNS WHO grade 4, and can be histologically or molecularly defined.

Although molecular testing is required for the diagnosis of these tumors, there are several surrogate IHC markers that can be used in lieu of the corresponding molecular test in routine practice. IHC is a cheaper technique and available in most of the laboratories. The neuropathology workup for adult-type diffuse gliomas starts with diagnostic IHC markers such as glial fibrillary acidic protein (GFAP), vimentin, and Olig2. Ki67(MIB1) is useful as a supportive marker for assessing the tumor grade. More recently, surrogate IHC markers (mutation-specific antibodies) such as IDH1 p.R132H, ATRX, and p53 are being used routinely as the first step in the diagnostic evaluation of adult-type diffuse gliomas.[12] IHC for IDH1 p.R132H is highly sensitive and specific as a surrogate for the corresponding mutation.

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The majority of IDH-mutant astrocytomas are positive for IDH1 p.R132H and show loss of ATRX expression with p53 immunopositivity. In a situation where IDH1 p.R132H is positive and ATRX shows a retained expression, testing for 1p/19q codeletion is advised to exclude oligodendroglioma.[13] *ATRX* mutations are mainly truncating mutations with occasional missense mutations in the highly conserved region of the helicase domain of the gene. These are associated with loss of ATRX nuclear expression by IHC.[13] *TP53* mutations are usually missense mutations which strongly associates with p53 nuclear immunopositivity. More than >10% nuclear positivity is shown to correlate with an underlying *Tp53* mutation.[13] However, non-missense mutations or stop codon mutations can show p53 negativity on IHC and therefore p53 nuclear immunopositivity is generally considered alongside with ATRX staining, 1p/19q codeletion status, and histomorphology.[14] Whenever IHC for IDH1 p.R132H yields a negative result, the other non-canonical *IDH1* and *IDH2* mutations have to be investigated by Sanger sequencing. In WHO CNS5, a combined histological and molecular grading criteria is applied to IDH-mutant astrocytoma, considering CDKN2A/B (cyclin-dependent kinase inhibitor 2A/B) homozygous deletion (HD) status.[8] Any grade 2 or 3 tumor harboring CDKN2A/B HD is upgraded to grade 4. CDKN2A/B status is routinely assessed by the FISH technique, while quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), and array or sequencing based methods are the other less used techniques.[15] The histomolecular profile of astrocytoma, IDH-mutant, is shown in **Fig. 7.1**.

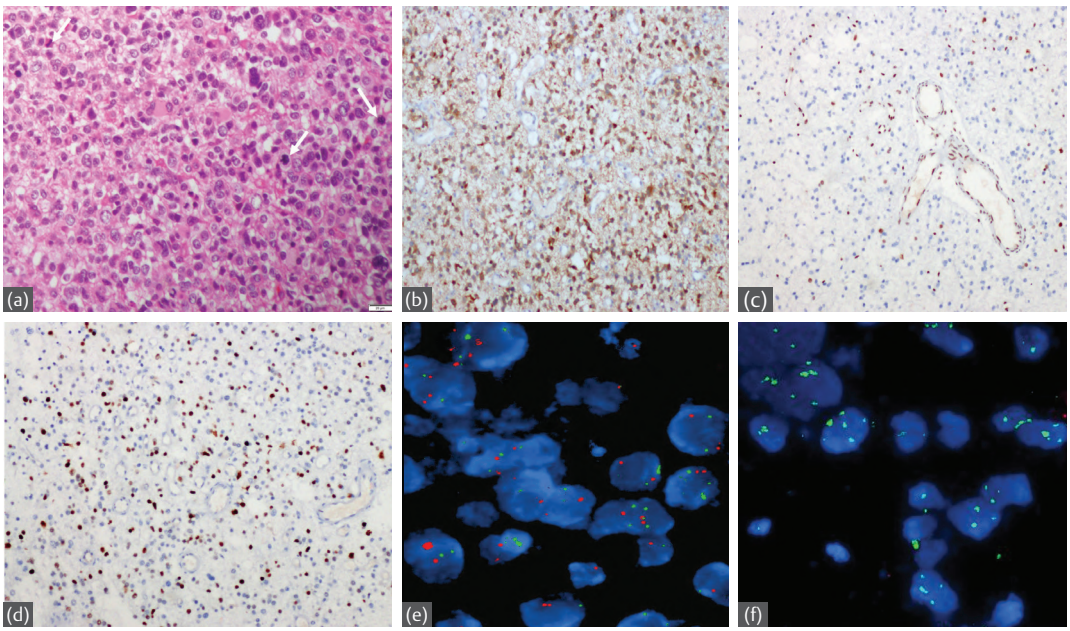

Fig. 7.1 Histomolecular profile of astrocytoma, IDH-mutant, CNS WHO grade 4. The tumor is predominantly diagnosed by an immunohistochemistry (IHC) panel, supplemented by fluorescent in situ hybridization (FISH) for molecular grading. The tumor is histologically grade 3 with increased mitosis (arrows), but with absent necrosis/microvascular proliferation **(a)** and is positive for IDH1p. R132H **(b)**, shows loss of ATRX **(c)**, and is p53 positive **(d)**. FISH shows CDKN2A/B homozygous deletion **(f)** compared to control **(e)**, thereby upgrading the tumor to CNS WHO grade 4. Original magnification ×200 **(a)** and ×100 **(b–d)**. FISH images—original magnification ×1000 **(e, f)**.

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The defining molecular alterations for oligodendroglioma include IDH mutation, assessed by IHC and/or DNA sequencing, and 1p/19q codeletion, which is routinely investigated by the FISH technique. Newer IHC surrogates are now being recognized for molecular alterations such as CDKN2A/B HD and 1p/19q codeletion. Methylthioadenosine phosphorylase (MTAP) and p16 have been identified as surrogates for CDKN2A/B while increased expression of Huntingtin interacting protein 1 related (HIP1R) negative vimentin expression and loss of H3p.K27me3 are established as surrogates for 1p/19q-codeleted oligodendrogliomas.[16–20] These markers can be used in the place of molecular testing when there is resource limitation. In WHO CNS5, the term glioblastoma is reserved for an IDH-wild type tumor. A negative IDH1 p.R132H by IHC in a patient ≥55 years of age is sufficient to designate the tumor as GBM, IDH-wild type, and Sanger sequencing for other IDH1/2 mutations is not required.[21] However, a negative IDH1 p.R132H by IHC in a patient <55 years of age necessitates Sanger sequencing for other IDH1/2 mutations. Furthermore, an IDH-wild type lower grade diffuse glioma that has at least one of the following molecular features is designated as GBM, IDH-wild type: TERT promotor mutation, EGFR gene amplification, and +7/–10 chromosome copy number changes.[3] MGMT promoter methylation status still remains the single most important prognostic factor and predictive marker to the action of temozolomide and helps guide treatment of particularly elderly patients with GBM or in the setting of recurrence.[22] Hence, testing for MGMT promoter methylation can be reserved for such patients, since it does not determine the use of temozolomide in all patients.

Therefore, it is evident that for adult-type diffuse gliomas, surrogate IHC markers can suffice in many cases to reach the diagnosis and molecular testing can be kept optional in most cases, while becoming mandatory in certain situations. Moreover, the WHO CNS5 allows pathologists to use the "layered/tiered" format, which combines histological and molecular data to provide the most optimal diagnosis. Even if a particular molecular test is not performed and histology and IHC markers are highly suggestive of the tumor type, a not otherwise specified (NOS) diagnosis can be offered with an appropriate comment and the patient can be treated accordingly. An example of a molecularly defined tumor and an NOS diagnosis in a "layered/tiered diagnosis" format is shown in **Table 7.1**.

Pediatric-Type High-Grade Gliomas

This group includes four tumor types that are molecularly defined: (1) diffuse midline glioma, H3K27-altered; (2) diffuse hemispheric glioma, H3G34-mutant; (3) diffuse pediatric-type high-grade glioma, H3/IDH-wild type (characterized by other molecular alterations such as *EGFR*, *MYCN*, and *PDGFRA* amplification, *TP53* mutations, and others); and (4) infant-type hemispheric glioma (characterized mostly by *ALK*, *ROS*, *MET*, and *NTRK* alterations).

Diffuse midline glioma (DMG), H3K27-altered, further includes DMG, H3K27M-mutant; DMG, H3-wild type with EZHIP overexpression; and DMG, EGFR-mutant. These three tumors uniformly show loss of expression of H3 p.K27me3 (H3 trimethylated protein), and hence are referred to as H3K27-altered tumors. Neuropathological workup for DMG starts by using the IHC marker H3p.K27me3. If there is loss of expression, it confirms the diagnosis of DMG, H3K27-altered. Following this, DMG, H3K27M-mutant, can be diagnosed using a surrogate IHC marker (H3p.K27M), and EZHIP serves as a surrogate for DMG with EZHIP overexpression. DMG, EGFR-mutant, is a rare bithalamic glioma and molecular testing for EGFR mutations is mandatory for the diagnosis of this tumor type.[23]

Similarly, H3p.G34R/V is a good surrogate IHC marker to diagnose diffuse hemispheric

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Table 7.1 Shows the layered/tiered format for reporting, taking an example of an oligodendroglioma

A: Depicts the complete diagnosis according to the guidelines of the WHO, since histological and molecular testing is complete

Site: Cerebral hemisphere	
Integrated diagnosis	Oligodendroglioma, IDH-mutant and 1p/19q codeleted
Histopathological classification	Oligodendroglioma
CNS WHO grade	2
Molecular information	Tumor is positive for IDH1p.R132H (IHC) and shows 1p/19q codeletion (FISH)

B: Depicts the NOS diagnosis since molecular workup is incomplete

Site: Cerebral hemisphere	
Integrated diagnosis	Oligodendroglioma, IDH-mutant, NOS
Histopathological classification	Oligodendroglioma
Histologic grade	2
CNS WHO grade	Not applicable since tumor is not molecularly characterized (histologic grade is provided)
Molecular information	By IHC, the tumor is positive for IDH1p.R132H FISH for 1p/19q codeletion could not be performed

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NOS, not otherwise specified.
Note: NOS diagnosis is just an alert to the clinician who can decide whether the patient can be treated at this level or further molecular testing is mandatory.

glioma, H3G34-mutant. However, diffuse pediatric-type high-grade gliomas, H3/IDH-wildtype, and infant-type hemispheric gliomas mandatorily require molecular testing for confirmation of the diagnosis. Another tumor type that is encountered in children and young adults is glioma in the setting of constitutional mismatch repair deficiency syndrome (cMMRD). There are antibodies available for the four mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) that can be used in routine settings.[24] On IHC, one or more MMR proteins show loss of expression in the tumor cells as well as native cells of the neuroparenchyma. Thus, wherever there is a high degree of suspicion, MMR proteins should be investigated. Other methods of testing include PCR for MicroSatellite instability (MSI) analysis, or NGS for germline mutations.

Therefore, many of the commonly occurring pediatric-type high-grade gliomas can be conveniently diagnosed using surrogate IHC markers, and molecular testing can be reserved for only a few tumors. **Table 7.2** details the recommended IHC markers and molecular tests that are optional or mandatory for pediatric-type diffuse high-grade gliomas, and **Fig. 7.2** shows some of the pediatric-type high-grade gliomas where an integrated WHO CNS5 diagnosis can be reached using IHC surrogate markers.

Pediatric-Type Diffuse Low-Grade Gliomas, Circumscribed Astrocytic Gliomas, and Glioneuronal Tumors

These groups are associated with chronic epilepsy. They are benign, and the majority correspond to CNS WHO grade 1 or 2 with a few exceptions. Patients generally have a good prognosis with complete surgical resection. The first step toward diagnosis is histologic assessment supported by diagnostic and/or surrogate IHC markers for tumor characterization. Since several tumor types in these groups are histologically defined,

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Table 7.2 Recommended IHC surrogates and molecular tests that are mandatory or optional for pediatric-type diffuse high-grade gliomas

Tumor type	Immunohistochemistry	Molecular tests/comments
Diffuse midline glioma (DMG), H3K 27-altered	H3 p.K27me3, H3p.K27M, EZHIP ATRX, p53 (useful for thalamic DMG)	(i) IHC surrogates suffice for the diagnosis of DMG, H3K27M-mutant, and DMG, H3-wild type with EZHIP overexpression (ii) DNA sequencing for EGFR mutation is mandatory for DMG, EGFR-mutant
Diffuse hemispheric glioma, H3G34- mutant	H3 p.G34R/V, olig2, ATRX, p53	(i) IHC surrogates suffice for the diagnosis (ii) DNA sequencing for H3.3 or MP is optional, useful for unresolved cases
Diffuse pediatric-type HGG, IDH-wild type/ H3-wild type	No specific IHC	DNA sequencing/FISH/NGS/MP mandatory for diagnosis
Infant-type hemispheric glioma	ALK, ROS, c-MET	(i) IHC surrogates are suggestive of diagnosis (ii) DNA sequencing/FISH/NGS/MP mandatory for diagnosis
HGG in the setting of cMMRD	MLH1, MSH2, MSH6, PMS1	(i) IHC surrogates are suggestive of diagnosis (ii) NGS is mandatory for diagnosis

Abbreviations: cMMRD, constitutional mismatch repair deficiency syndrome; FISH, fluorescent in situ hybridization; HGG, High grade glioma; IHC, immunohistochemistry; MP, methylation profiling; NGS, next generation sequencing.

wherever possible, the most specific histologic diagnosis can be rendered, particularly in tumors with classic morphology; example being pilocytic astrocytoma, CNS WHO grade 1. However, some of the low-grade glial and glioneuronal tumors can have overlapping histologic features and ancillary molecular tests may be required to provide a definitive WHO diagnosis. In such cases, a broader diagnosis of "low-grade glial/glioneuronal tumor, NOS" can be provided. A point to note is that sometimes there can be overlapping molecular alterations such as *BRAFp.V600E* mutations, among histologically different tumor types in these groups. Conversely, there are some tumors which cannot be diagnosed on histology alone. One example is diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC), which is a provisional tumor type that has entered the classification. The histological feature of this tumor overlaps with oligodendroglioma and other glial/glioneuronal tumors and requires methylation profiling for a definitive diagnosis. Taken together, most of the low-grade gliomas/glioneuronal tumors can be diagnosed on the basis of histology and IHC, and further molecular testing can be kept optional and carried out only if it has a direct bearing on the treatment regimen.

Ependymomas

Ependymoma classification has always been fraught with difficulties since histopathological grading was challenging and overlayed with poor interobserver reproducibility, even when screened by the most experienced neuropathologists. Hence, molecular parameters were considered in the WHO 2016 classification itself. In WHO CNS5, ependymomas are classified based on the anatomical location of the tumor and underlying molecular alterations which reflect the biology of these tumors. The molecularly defined tumor types include: (1) supratentorial ependymoma (ST-EPEN), *ZFTA* fusion-positive; (2) ST-EPEN,

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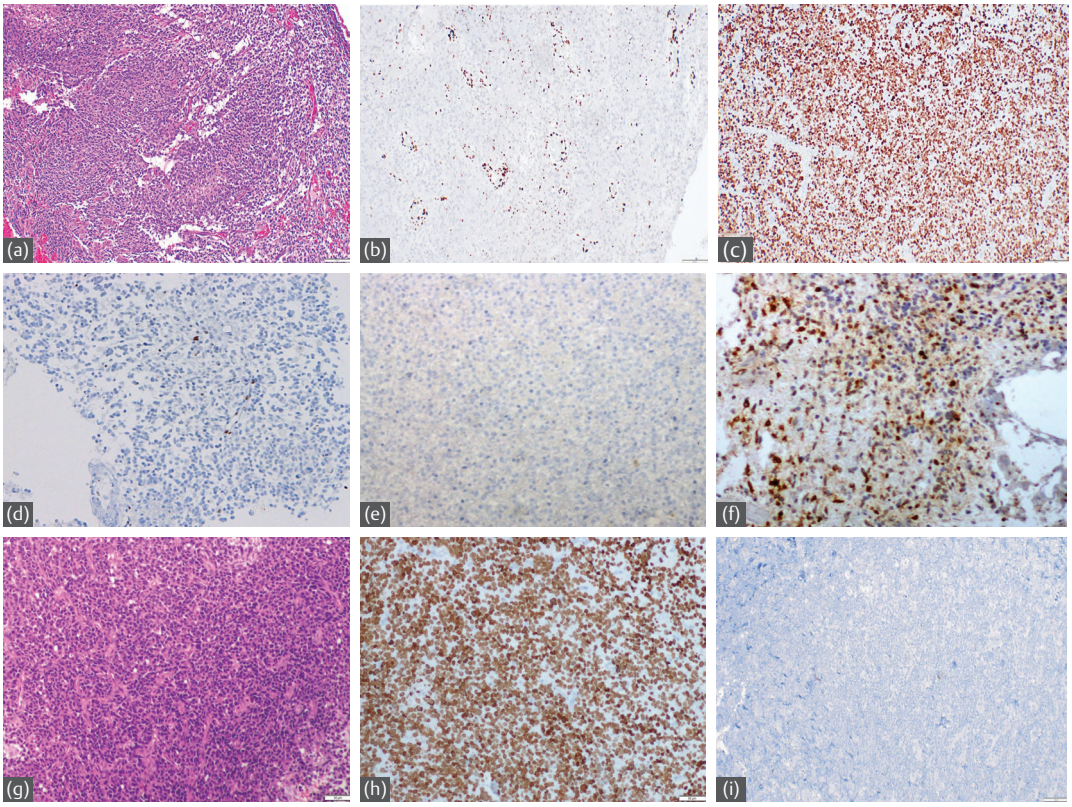

Fig. 7.2 Pediatric-type high-grade gliomas where an integrated WHO CNS5 diagnosis can be provided by using an immunohistochemistry (IHC) panel. **(a–c)** Diffuse midline glioma, H3K27M-mutant. Histologically, it is a high-grade glioma **(a)** and shows loss of H3p.K27me3 **(b)** and is positive for H3p.K27M **(c)**. **(d–f)** Diffuse midline glioma, H3-wild type with EZHIP overexpression. The tumor shows loss of H3p.K27me3 **(d)**, is negative for H3p.K27M **(e)**, and positive for EZHIP **(f)**. **(g–i)** Diffuse hemispheric glioma, H3G34-mutant. Histologically, it is a high-grade glioma composed of undifferentiated glial cells **(g)** and is positive for H3p.G34R **(h)** and negative for H3p.G34V **(i)**.

YAP1 fusion-positive; (3) posterior fossa group A (PFA) ependymoma; (4) posterior fossa group B (PFB) ependymoma; and (5) spinal ependymoma, *MYCN*-amplified. In addition, supratentorial/posterior fossa/spinal ependymoma as well as subependymoma and myxopapillary ependymoma can be histologically defined as per the WHO CNS5 classification. Molecular testing is required for the diagnosis of the molecularly defined ependymomas. Fortunately, there are surrogate IHC markers that can be used. In some tumor types, such as PFA, the WHO diagnosis can be reached using one surrogate IHC marker, i.e., H3p.K27me3. EZHIP is an additional useful marker. In the others, the surrogate IHC marker(s) help suggest the most probable diagnosis although a definitive WHO diagnosis cannot be offered without the required molecular test. For example, by using two surrogate IHC markers, L1CAM and p65, a diagnosis of ST-EPEN, *ZFTA*-fusion positive, can be suggested although definitive diagnosis requires molecular testing to demonstrate gene fusion for *ZFTA* (c11orf95), as per WHO CNS5. On the other hand, there are no IHC surrogates for ST ependymoma, *YAP1* fusion-positive, and diagnosis depends

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on demonstrating gene fusion for *YAP1*. Also, PFB ependymomas require methylation profiling for a definitive diagnosis.[25] Supratentorial and posterior fossa ependymomas that are not molecularly characterized, either because molecular testing was not performed or molecular testing was done but the results were inconclusive, are assigned the suffixes NEC (not elsewhere classifiable) or NOS, respectively. In such a situation, a layered/tiered approach can provide useful information although a NOS/NEC diagnosis is provided, and these tumors are graded as 2 or 3 based on histology. Spinal ependymoma, *MYCN*-amplified tumors almost always have a grade 3 histology.[26] Here, the molecular testing can be reserved only for grade 3 tumors. **Fig. 7.3** depicts a simplified and practical approach for the diagnosis of ependymoma in routine practice.

Embryonal Tumors

Medulloblastoma

Medulloblastomas (MBs) are the most common malignant pediatric brain tumor constituting about 20% of all tumors in this age group and more than two-thirds of embryonal tumors. In WHO CNS5, MBs are classified as MB, molecularly defined, and MB, histologically defined. Molecularly defined MBs include MB, WNT-activated; MB, SHH-activated and *Tp53* wild type; MB, SHH-activated and *Tp53* mutant; and MB, non-WNT/non-SHH (which includes group 3 and group 4). Currently IHC surrogates such as β-catenin, GAB1, YAP1, and p53 are sufficient to identify these molecular groups of MB.[27,28] WNT-activated MBs express β-catenin and YAP1, SHH-activated MBs express GAB1 and YAP1, and group 3 and group 4 MBs are immunonegative for β-catenin, GAB1, and YAP1. p53 IHC is essential in diagnosing SHH-activated and *Tp53*-mutant MBs. However, for the detection of group 3 and group 4, molecular tests such as FISH, DNA sequencing, Nanostring etc. are required. However, these tests can be kept optional unless requested from the treating oncologist.

Other CNS Embryonal Tumors

IHC surrogates play a very important role in diagnosing tumor types in this group. INI1 and BRG1 are surrogate IHC markers that

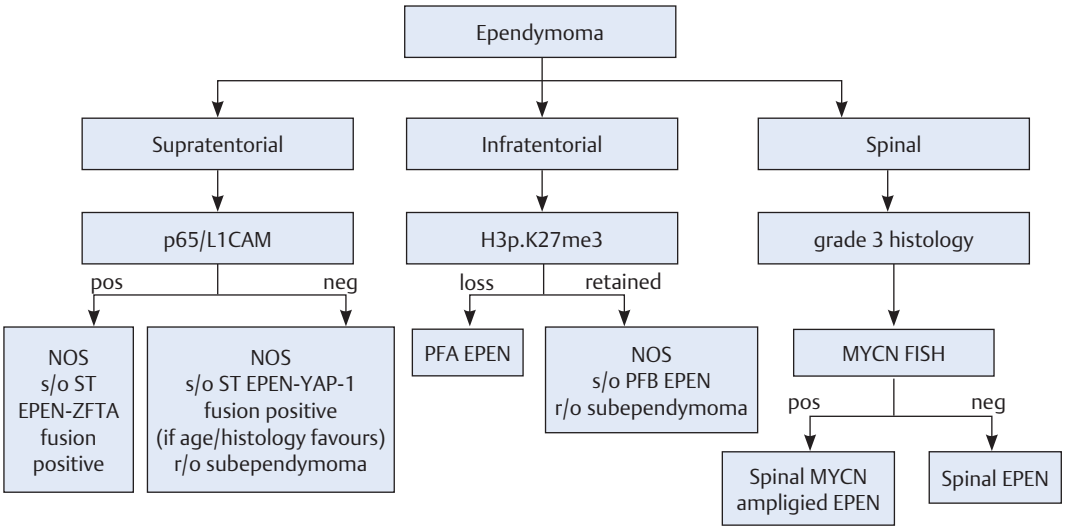

Fig. 7.3 A simplified algorithm to diagnose ependymomas using mainly immunohistochemistry (IHC) markers and fluorescence in situ hybridization (FISH) when required.

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can provide a definite diagnosis of atypical teratoid/rhabdoid tumor (AT/RT). LIN28A is a sensitive although not a specific marker for embryonal tumor with multilayered rosettes (ETMR), and for a definite WHO diagnosis the specific molecular alterations (C19MC amplification or DICER1 mutation) have to be demonstrated.[29] CNS neuroblastoma, FOXR2-altered, is a newly introduced tumor type that can be diagnosed only by methylation profiling.[27] However, recent studies have shown that by IHC positivity for Olig2, synaptophysin, and SOX10 with negative vimentin expression along with 1q gain demonstrated by FISH in combination are very specific surrogates for CNS neuroblastoma, FOXR2-altered.[30] Similarly, BCOR immunopositivity is highly suggestive of CNS tumor with BCOR internal tandem duplication, although the specific diagnosis is established by DNA sequencing.[27,31] INI1 loss by IHC is also a specific marker for the diagnosis of cribriform neuroepithelial tumor (CRINET). By and large, it is evident that surrogate IHC markers can provide a definitive diagnosis or can suggest the "most probable" diagnosis in this group.

Conclusion

Molecular testing is a necessity for optimal patient care in many brain tumors. However, the testing platforms have to be strategically selected so that it provides accurate diagnosis and is useful for prognostication and to improve patient outcome. There are two approaches for this: (1) A stepwise approach starting with IHC and then proceeding to perform simple molecular test such as FISH, PCR, or Sanger sequencing is recommended. It is important that the choice of IHC markers and molecular tests are decided by an experienced neuropathologist. Thorough histological examination is pivotal in a given case and based on this, the neuropathologist can decide on further molecular testing options. (2) The second approach is to carry out a high-throughput technique using platforms such as NGS or methylation profiling. Such tests are particularly useful in diagnostically challenging cases which would otherwise require a battery of IHC and several molecular tests to detect genetic/epigenetic alterations.

However, implementing molecular testing for brain tumor diagnosis has significant challenges in several countries, particularly the lower middle-income countries (LMICs), mainly due to economic and technical barriers. LMICs have a varied range of facilities, wherein some centers are capable of providing molecular diagnosis and others are not. Hence, molecular testing can be stratified based on the tumor type and the available resources. In view of this, the group comprising experienced neuropathologists from the Asian Oceanian Society of Neuropathology (AOSNP) has tried to develop strategies to provide resource-stratified recommendations for the diagnosis of commonly occurring brain tumors under the banner of "ADAPTR" (Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Limited Regions). The goal of ADAPTR is to put forth practical recommendations for the approach to the diagnosis of these tumors based on available resources, while not deviating from the WHO guidelines.[32] The recommendations will place emphasis on histology and IHC approaches while keeping molecular testing mainly optional, unless it is mandatorily required.

References

1. Bailey P, Cushing H. A classification of the tumours of the glioma group on a histogenetic basis, with a correlated study of prognosis. Medium 8vo. Pp. 175, with 108 illustrations. 1926. Philadelphia, London, and Montreal: J. B. Lippincott Company. 21s. net. (1927). British Journal of Surgery, 14(55), 554–555.
2. Louis DN, Wesseling P, Paulus W, et al. cIMPACT-NOW update 1: Not Otherwise Specified (NOS) and Not Elsewhere Classified (NEC). Acta Neuropathol 2018;135(3):481–484

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3. Louis DN, Giannini C, Capper D, et al. cIMPACT-NOW update 2: diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant. Acta Neuropathol 2018;135(4):639–642
4. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV." Acta Neuropathol 2018;136(5):805–810
5. Ellison DW, Hawkins C, Jones DTW, et al. cIMPACT-NOW update 4: diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or $BRAF^{V600E}$ mutation. Acta Neuropathol 2019;137(4):683–687
6. Louis DN, Wesseling P, Aldape K, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol 2020;30(4):844–856
7. Ellison DW, Aldape KD, Capper D, et al. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. Brain Pathol 2020; 30(5):863–866
8. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol 2020;139(3):603–608
9. Capper D, Stichel D, Sahm F, et al. Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: the Heidelberg experience. Acta Neuropathol 2018;136(2):181–210
10. Viaene AN. Pediatric brain tumors: a neuropathologist's approach to the integrated diagnosis. Front Pediatr 2023;11:1143363
11. Ellison DW. WHO Classification of Tumours Editorial Board. Central Nervous System Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer; 2021
12. Whitfield BT, Huse JT. Classification of adult-type diffuse gliomas: impact of the World Health Organization 2021 update. Brain Pathol 2022; 32(4):e13062
13. Santosh V, Rao S. A review of adult-type diffuse gliomas in the WHO CNS5 classification with special reference to astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant and 1p/19q codeleted. Indian J Pathol Microbiol 2022; 65(Suppl):S14–S23
14. Takami H, Yoshida A, Fukushima S, et al. Revisiting TP53 mutations and immunohistochemistry—a comparative study in 157 diffuse gliomas. Brain Pathol 2015;25(3):256–265
15. Chai R, Fang S, Pang B, et al. Molecular pathology and clinical implications of diffuse glioma. Chin Med J (Engl) 2022;135(24):2914–2925
16. Brcic L, Le Stang N, Gallob F, et al. A combination of MTAP and p16 immunohistochemistry can substitute for CDKN2A fluorescence in situ hybridization in diagnosis and prognosis of pleural mesotheliomas. Arch Pathol Lab Med 2023;147(3): 313–322
17. Chapel DB, Schulte JJ, Berg K, et al. MTAP immunohistochemistry is an accurate and reproducible surrogate for CDKN2A fluorescence in situ hybridization in diagnosis of malignant pleural mesothelioma. Mod Pathol 2020;33(2):245–254
18. Felix M, Friedel D, Jayavelu AK, et al. HIP1R and vimentin immunohistochemistry predict 1p/19q status in IDH-mutant glioma. Neuro-oncol 2022; 24(12):2121–2132
19. Filipski K, Braun Y, Zinke J, et al. Lack of H3K27 trimethylation is associated with 1p/19q codeletion in diffuse gliomas. Acta Neuropathol 2019;138(2):331–334
20. Geyer L, Wolf T, Chenard MP, et al. p16 immunohistochemical expression as a surrogate assessment of CDKN2A alteration in gliomas leading to prognostic significances. Cancers (Basel) 2023; 15(5):1512
21. Antonelli M, Poliani PL. Adult type diffuse gliomas in the new 2021 WHO classification. Pathologica 2022;114(6):397–409
22. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003
23. Rao S, Sahay A, Epari S. Paediatric type diffuse high grade gliomas in the WHO CNS5 classification: what the pathologist needs to know? Indian J Pathol Microbiol 2022;65(Suppl):S50–S58
24. Carrato C, Sanz C, Muñoz-Mármol AM, et al. The challenge of diagnosing constitutional mismatch repair deficiency syndrome in brain malignancies from young individuals. Int J Mol Sci 2021;22(9):4629
25. Gupta RK, Sharma A, Sharma MC. Overview of recent advances in the classification of ependymomas in WHO CNS5 classification:

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simplified approach to their integrated diagnosis. Indian J Pathol Microbiol 2022;65(Suppl):S68–S72
26. Rao S, Sugur H, Konar S, Arivazhagan A, Santosh V. MYCN amplification in spinal ependymoma: a five-year retrospective study. Neuropathology 2023;43(6):457–462
27. Gianno F, Miele E, Antonelli M, Giangaspero F. Embryonal tumors in the WHO CNS5 classification: a review. Indian J Pathol Microbiol 2022;65(Suppl): S73–S82
28. Santosh V, Rao S, Dasgupta A, Gupta T. Diagnosis and management of central nervous system embryonal tumors in the molecular era: a contemporary review. International Journal of Neurooncology 2021;4(Suppl 1):S190–S205
29. Rao S, Rajeswarie RT, Chickabasaviah Yasha T, Nandeesh BN, Arivazhagan A, Santosh V. LIN28A, a sensitive immunohistochemical marker for embryonal tumor with multilayered rosettes (ETMR), is also positive in a subset of atypical teratoid/rhabdoid tumor (AT/RT). Childs Nerv Syst 2017;33(11):1953–1959
30. Tauziède-Espariat A, Figarella-Branger D, Métais A, et al; the RENOCLIP-LOC. CNS neuroblastoma, FOXR2-activated and its mimics: a relevant panel approach for work-up and accurate diagnosis of this rare neoplasm. Acta Neuropathol Commun 2023;11(1):43
31. Rao S, Mitra S, Sugur H, et al. Central nervous system high grade neuroepithelial tumor with BCOR immunopositivity: is there a molecular heterogeneity? Brain Tumor Pathol 2021;38(1):41–49
32. Buckland ME, Sarkar C, Santosh V, et al. Announcing the Asian Oceanian Society of Neuropathology guidelines for Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Restrained Regions (AOSNP-ADAPTR). Brain Pathol 2024; 34(2):e13201

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8 Gamma Knife Radiosurgery for High-Grade Gliomas

Shweta Kedia, Sarvesh Goyal, and Deepak Agarwal

Introduction

Gamma knife radiosurgery (GKRS) is an acceptable mode of treatment for many intracranial pathologies. However, its role in gliomas is controversial. WHO 2021[1] classification refers to grade 3 and grade 4 as high-grade gliomas (HGGs) and they constitute the most common primary and aggressive brain tumor. Surgical[2] resection followed by external beam radiation with concurrent and adjuvant chemotherapy is currently the accepted standard of care. It is highly resistant to treatment and has very poor prognosis with survival of between 15 and 21 months. The patients who survive come back with recurrence almost within a year of treatment. There are no fixed protocol regime for these recurrent tumors.

Recently, GKRS has been much discussed as one of the radiation modalities for HGGs. There are retrospective data and institutional studies to suggest its use as adjuvant therapy post surgical resection in primary HGGs. It is also considered as a salvage therapy in recurrent HGG and as neoadjuvant therapy in few cases.

GKRS is a noninvasive technique which delivers high doses of ionizing radiation over one to five sessions in a conformal manner to the tumor, sparing nearby healthy tissues. By delivering the high dose rate with a rapid fall, it attacks the tumor tissue while preserving the relatively radioresistant normal brain cells. It induces apoptosis in proliferating cells, enhances CD8+ T cell response against tumor, reduces the brain edema and possibility of leptomeningeal damage, and gives better quality of life. It makes surgical resection more effective by reducing the vascularity and tumor size, thereby making it more accessible and reducing surgical morbidity. Creation of hotspots because of in-homogenous distribution of dose within the target takes care of the relatively hypoxic cells and induces rapid apoptosis in sublethally injured zones. In this chapter we shall review the role of GKRS in HGG, the planning technique of GKRS, and the associated complications.

Role of GKRS in HGG

Adjuvant Therapy in Primary HGG

The aim of treating HGG is to strike a balance between the duration of survival and quality of life. Recurrence in HGG is a rule and it typically occurs within the 2-cm margin of the tumor bed. This is exploited to treat the HGG with radiosurgery.[3] In the only multicenter randomized trial on HGG using stereotactic radiosurgery (SRS) (GKRS or LINAC) where patients were divided into two arms of standard treatment with and without SRS along with concurrent chemotherapy (carmustine), there was no benefit observed in the overall survival of the patients in either group.[4] In this study SRS was given 1 week prior to external beam radiation therapy (EBRT) in the trial arm. However, this study had excluded the patients undergoing gross total resection and did not take into consideration the role of GKRS as boost therapy post conventional radiation. In the study where GKRS was used as an elective treatment regime 4 weeks after EBRT, a significant improvement in the overall survival of these patients was observed.[5] The patients with a good Karnosky

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performance status (KPS) of more than 80 and those who have received chemotherapy are the ones who are more likely to benefit from the boost therapy of SRS. Boost therapy had an advantage of radiobiology as it targeted the remaining repopulating cancer cells. Combining temozolomide instead of carmustine with GKRS reduces the radiation-induced invasiveness of glioma and therefore is the preferred chemotherapeutic agent.

GKRS may be offered as an adjuvant therapy either 1 week prior to EBRT, or boost therapy within 4 weeks of EBRT.[6] There are proponents who favor giving GKRS as stand-alone radiation along with temozolomide regime. In these cases, the patients are taken up as an ultra-early candidates within 3 days post-surgery. In one of our institutional studies ambispective analysis was done for the patients operated for HGG.[7] They were grouped into two categories, one with GKRS within 4 weeks of surgery and lifelong temozolomide while the other arm constituted of conventional radiation within 6 weeks followed by concurrent and adjuvant temozolomide. No significant difference in the progression-free and overall survival was observed. This study proved the noninferiority of GKRS over EBRT as a stand-alone radiation technique for HGG.

Technique of GKRS

When the patient is identified with a confirmed diagnosis of HGG based on biopsy, the patient undergoes MRI of brain (T1, T2, contrast, and fluid-attenuated inversion recovery [FLAIR] sequences). The patient then undergoes frame fixation or frameless, which is decided based on the patient's general condition and volume of the tumor. The stereotactic image is then acquired and fused with MRI. The contrast-enhanced portion is delineated as target. The integration of 11-C methionine PET to delineate the tumor may further enhance the target delineation. The metabolic volume of the tumor may be larger than the contrast-enhancing portion. Treatment plan is then generated using the gamma plan. The prescribed dose ranges between 10 and 20 Gy, lower dose for larger tumor volume. Multiple iso-centric shots are then placed to get good conformality index and coverage (**Fig. 8.1**). Post GKRS, patients are given decongestant and steroid therapy based on existing edema.

Recurrent HGG

The treatment options for recurrent GBM includes redo surgery, chemotherapy, bevacizumab, re-irradiation, and targeted therapy. GKRS helps in giving higher dose to the target while minimizing side effects.[8] It has been suggested as a salvage therapy in small, focal and nodular recurrence. For larger lesions as well, people have given hypo-fractionated GKRS and showed improvement in progression-free and overall survival.[9,10] However, there is a higher risk of adverse reactions. There are studies showing that complementing GKRS with molecular targeted therapies like matrix metalloproteinase inhibitor and epidermal growth factor inhibitors did not show improvement in overall survival. Addition of bevacizumab therapy after GKRS reduces radiation-induced changes while improving overall survival. Distant tumor progression occurred in almost 75% of the patients, yet the local control rate is around 72%.

As Neoadjuvant Therapy in HGG

Preoperative stereotactic GKRS has advantages like better tumor control, reduction of tumor size and vascularity, lower risk of leptomeningeal disease, lower rates of radionecrosis of adjoining brain, and enhancing antitumor immunity. It can simultaneously address the various hotspots of the tumor. It allows for DNA repair pathways and better micro involvement around the tumor. However, it lacks sensitivity and is therefore not recommended.

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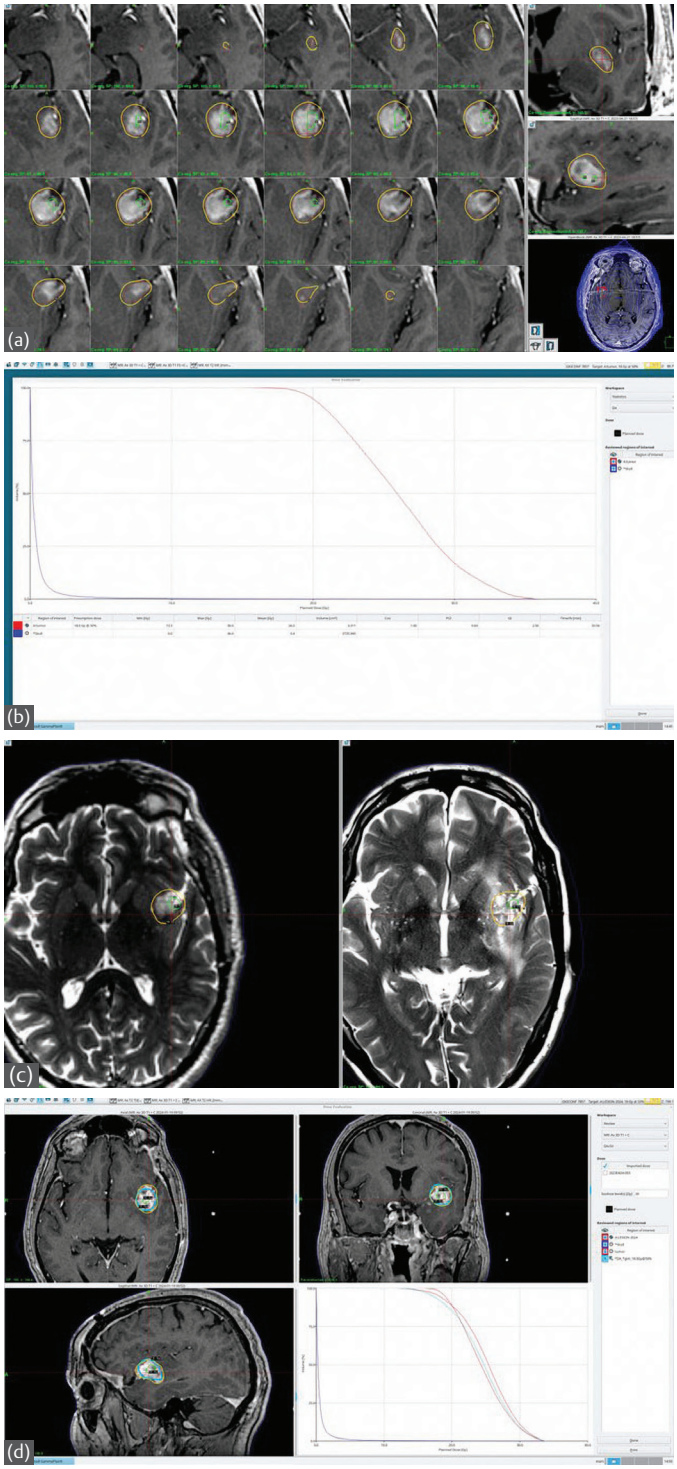

Fig. 8.1 Imaging and gamma plan of a 60-year-old male operated for left insular high-grade glioma. Biopsy was glioblastoma, IDH-wild type, CNS WHO grade 4 with MIB index of 10 to 15% in the highest proliferating area. IDH wild type, ATRX retained, and p53 present in 20% of the cells. He was taken up for gamma knife radiosurgery (GKRS) as an adjuvant therapy at 2 weeks post-surgery with concurrent temozolomide. **(a)** Gamma plan of the patient. 18 Gy at 50% was delivered at the tumor margin shown by the yellow line. **(b)** The dose distribution curve across the tumor volume. A volume of 3.3 cc with a mean dose of 26 Gy and 100% coverage of the tumor. **(c)** The comparative T2 axial scan at the follow-up of 1 year shows mild increase in the tumor volume which was confirmed on perfusion scan. **(d)** The patient was taken up for repeat GKRS at the end of 1 year. The blue line represents the previous tumor margin. A repeat dose of 18 Gy at 53% isodose line was given over 25 minutes. The patient is still under follow-up and repeat imaging at 6 months from the last GKRS is planned.

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Complications

Use of radiosurgery in HGG is based on level III evidence. The treatment protocol for metastasis with GKRS was based on better cognitive profile in these patients when compared to that of conventional radiotherapy group. The same has been observed in HGG group as well. The adverse radiation effect in this group is prevalent in 90% of the cases in different grades. The patients may present with edema surrounding the tumor bed. This is unrelated to the total dose and could also be a marker of tumor progression. The associated edema and radiation changes that may follow the GKRS are managed with steroids and occasionally bevacizumab. The progression-free survival counted from the time of GKRS to the progression of disease is variable and is documented to be around 15 to 16 months.

Key Points

- There are no standardized selection criteria for the patients with HGG for radiosurgery.
- Smaller tumor volume <10 cc, unifocal with a higher KPS and younger age shows better response.
- Identifying IDH wild type, 1p19q codeletion, and other markers which are indicators of radiosensitivity could help in improvising the selection criteria.
- For lesions more than 3.5 cm and located in the functional area, fractionated radiosurgery is given.
- GKRS after conventional therapy as boost to the tumor bed within 6 weeks of EBRT gives better overall survival.
- GKRS has been found to be safe and effective for recurrent HGG.
- Patients receiving GKRS at the time of progression rather than at the time of initial treatment shows better survival.
- GKRS in newly diagnosed HGG is not recommended.
- Management of glioma requires a multidisciplinary neuro-oncology group.

Conclusion

GKRS is a noninvasive adjunct to surgery or radiotherapy in HGGs. It enhances survival and minimizes adverse effects of radiation. It can be useful in recurrent and metastatic tumors when used with chemotherapy or biological therapy. It can be used either preoperatively or postoperatively. The benefits and limitations require validation as trials are still on-going at various institutions.

References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-oncol 2021;23(8): 1231–1251
2. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987–996
3. De Bonis P, Anile C, Pompucci A, et al. The influence of surgery on recurrence pattern of glioblastoma. Clin Neurol Neurosurg 2013;115(1):37–43
4. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys 2004;60(3):853–860
5. Nwokedi EC, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. Neurosurgery 2002;50(1):41–46, discussion 46–47
6. Valerio JE, Wolf A, Wu X, et al. Assessment of gamma knife stereotactic radiosurgery as an

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adjuvant therapy in first-line management of newly diagnosed glioblastoma: insights from ten years at a neuroscience center. Int J Transl Med 2024;4(2):298–308

7. S Rai HI, Agrawal D, Singh M, Kale SS. Early gamma knife therapy (without EBRT) in operated patients of glioblastoma multiforme. Neurol India 2023;71(Suppl):S183–S188
8. Sun Y, Liu P, Wang Z, Zhang H, Xu Y, Hu S, Yan Y. Efficacy and indications of gamma knife radiosurgery for recurrent low-and high-grade glioma. BMC cancer. 2024 Jan 5;24(1):37.
9. Scaringi C, Enrici RM, Minniti G. Combining molecular targeted agents with radiation therapy for malignant gliomas. Onco Targets Ther. 2013; 6:1079–95.
10. Kulinich, D. P., Sheppard, J. P., Nguyen, T., Kondajji, A. M., Unterberger, A., Duong, C., et al. Radiotherapy versus combination radiotherapy-bevacizumab for the treatment of recurrent high-grade glioma: a systematic review. Acta Neurochir. 2021 163 (7), 1921–1934. doi:10.1007/s00701-021-04794-3

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9 Mechanical Thrombectomy in Acute Stroke: India Is Still Far Behind

Deep Das, Uddalak Chakraborty, and Shashvat Desai

Introduction

Large vessel occlusions (LVOs) leading to stroke is one of the foremost causes of morbidity and mortality worldwide. Despite the recent advances and giant leap in neurovascular intervention in the past few decades, India tends to fall short of standard of care in acute stroke leading to adverse stroke outcomes. There is a marked disparity in global access to stroke thrombectomy attributable to a number of factors, which needs to be mitigated by adopting goal-directed strategies in order to reduce the burden and its implications inflicted by acute ischemic stroke.

Epidemiology

The lifetime risk of stroke has exponentially increased by 50% over the last 17 years, and from 1990 to 2019, there was an alarming rise of nearly 70% in stroke incidence and 102% increase in stroke prevalence. About 43% deaths attributable to stroke and 143% increase in disability adjusted life years (DALY) speak volumes on the impact of stroke on global health.[1] The bulk of the global stroke burden is contributed by lower and lower middle-income countries, and India is not an exception. The economic burden of stroke is also noteworthy, accounting up to 1.7% of global GDP[2] and almost 54 billion US dollars in terms of Indian economy. Large artery atherosclerosis in Asian population has been increasingly identified as a cause of acute ischemic stroke; large prospective studies have identified acute LVO as a leading contributor to post-stroke disability and mortality. Depending on the definition, LVOs account for 10 to 46% of ischemic strokes, and these patients are eligible for mechanical thrombectomy (MT) if they satisfy the inclusion criteria.[3] The fatality rate is as high as 30% and the stroke survivors tend to suffer from moderate to severe disability, hampering independent life. Restoration of cerebral perfusion by mechanical or pharmacological means tends to limit the disability and poor functional outcome after stroke, thus necessitating increased access to MT at a population level.

Definition of the Problem

Low- and middle-income countries account for around 85% of stroke mortality and post-stroke disability worldwide. The cumulative incidence of stroke has ranged from 108 to 172 per 100,000 per year, and the crude prevalence of strokes accounts for 44.3 to 559 per 100,000 over the last decade in India based on various population-based stroke registries.[4] The mean age of patients suffering from stroke in India is around 55 to 60 years which is nearly 10 years less compared to western population resulting in an increased burden of post-stroke disability.[5] Despite the advent of intravenous thrombolysis and MT which have dramatically changed the management of acute ischemic stroke worldwide, the proportion of eligible patients receiving thrombolysis and MT in India is abysmally low. Even with improving rates of stroke thrombolysis over the years with increased awareness, there is paucity

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of data on management of LVO stroke in India. There is also a distinct disparity in stroke incidence and prevalence as well as management in urban and rural areas of India. A significant delay has been reported in rural patients with acute stroke reaching hospital compared to urban population in India leading to prehospital delay which is an important barrier to time-sensitive stroke management in India. In the western world emergency medical services (EMSs) are endowed with the responsibility of rapid transfer of the patients to the stroke-ready hospitals, which is alarmingly low in comparison to the population catered by them in India.[6]

Mission Thrombectomy 2020 (MT2020) announced by The Society of Vascular and Interventional Neurology (SVIN) in 2016 identified the large gap between patients eligible for MT and patients receiving MT and proposed certain strategies to enhance efforts in streamlining affordable stroke care, thus improving access to MT.[7]

Barriers

- Disparity in access to MT: Access to MT is suboptimal even after so many years of the landmark trials with conclusive evidence on efficacy of this time-sensitive treatment modality. There is an obvious uneven distribution of global access to MT, which is further exacerbated by the disproportionate stroke burden in low- and middle-income countries. Per capita gross national income, prehospital LVO detection and referral to stroke-ready centers, availability of MT operator and center, and cultural barriers are some of the significant determinants of MT access worldwide.[8] A South Asia–specific regional analysis revealed that regional MT access (MTA) was 4.7 times less than the global median MTA; median MTA of India is around 1.83% compared to 2.79% worldwide. The relatively higher MT operator and center availability in India in South Asia and the Pacific Region appears to be a ray of hope.
- Absence of a national stroke registry protocol: Nationwide stroke registry is an absolute need of the hour to obtain specific information on the quantity as well as the quality of stroke care in India, which may help to implement and formulate policymaking. In order to offer affordable stroke care for all, it is instrumental to define the incidence and prevalence of stroke in rural and urban areas, and assess MT operator and center availabilities.
- Mismatch between demand and supply: Among 1,500,000 acute ischemic strokes in India, 375,000 are LVOs amounting to a financial burden of 54 million US dollars.[9] Around 270,000 patients per year are eligible for MT and the approximate number of MTs in our country ranges from 1080 to 1462 per year.[10] The alarmingly low number of neurointerventionalists trained in MT to cater to the patients with LVO eligible for MT is approximately 92.5 per 100,000 LVOs. India has just over 100 MT capable stroke centers compared to the demand of approximately 1500. The neurointerventionalists are predominantly based in urban areas with an unequal distribution across various states—the southern states having significantly higher number of neurointerventionalists compared to all the other regions.
- Perception: In the Indian scenario, around 75% of the urban patients tend to reach the hospital 3 hours after onset of stroke and rural patients take more than 24 hours on an average to receive medical any aid; hence, data on onset to door timings are not very much optimistic.[7] The rural healthcare system is incapable of prompt triage of LVO, which mandates time-sensitive referral

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to thrombectomy-capable centers. There is indeed a lack of awareness and an inertia among healthcare professionals in identification of this subset of stroke. Moreover, referral to health centers with inadequate stroke management facilities lead to loss of valuable time. A large subset of patients with LVO have a stuttering course and history of transient ischemic attacks, which are usually self-resolving; thus, they tend to seek medical help quite late in the course of disease, at times even after enduring a disabling neurodeficit. This highlights the essential role of extensive training of healthcare professionals on identification of symptoms of stroke as well as awareness programs among the general population.

- Unmet needs: The inclusion of CT angiography (CTA) in early stroke triaging would be extremely beneficial in referring patients to stroke-ready centers. With constant emphasis on choosing the suitable patient for MT, installation of improved imaging modalities and perfusion-based imaging is a significant barrier.
- Financial strain: Despite the resounding success of MT for LVO in five landmark randomized control trials, the feasibility of replicating these results in resource-limited setups of low- and middle-income countries is quite questionable. Given similar concerns expressed by the Brazilian government in 2018, a randomized controlled trial (RESILIENT trial) was conducted to demonstrate safety and efficacy of MT in middle-income country resource environment. Consequently, the success of the RESILIENT trial led to government-mandated reimbursement of MT as the standard of care for LVO stroke.[11] As per NHS data, approximate expenditure for stent retrievers used in MT range from 1936 to 6453 GBP.[12] In the Indian scenario, the procedure may cost around INR 400,000 to 500,000 on an average, which exceeds the average per capita income of 172,276 per year.[13] Although some government schemes provide financial assistance for these procedures, these schemes are still underpowered to cover the cost of MT in a large scale. Majority of the people belonging to lower socioeconomic strata lack medical insurance and those who are insured are unable to bear the huge expenses despite presence of resources at a stroke-ready center.[14] Apart from Sri Lanka, no other country in South Asia provides a defined reimbursement policy.

The data reflecting India's access to MT are based on units of stent retriever used; however, in real-world experience it is a tad bit more than recorded, as many laboratories reuse the instruments after reprocessing and sterilization.

An Effective Approach: Way Forward?

An effective approach to cater to this problem revolves around an effective device available at an affordable cost and an effective system to make stroke care affordable in India. Some large-scale cost utility analysis revealed that in the long run MT had a 99.9% probability for quality-adjusted life years compared to standard medical management.[15]

- Effective device at an affordable cost: A cost-effective SuperNova (Gravity, California, USA) stent retriever, characterized by double-fusiform cell technology, has the potential for superior efficacy with red and white clots compared to available Solitaire-X stent retriever.[16]

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- Effective approach: No clinical trial has been carried out in India to evaluate a novel cost-effective thrombectomy device. GRASSROOT trial is an ongoing prospective study investigating an endovascular revascularization device which may be instrumental eventually to provide affordable thrombectomy to eligible patients in an Indian scenario.[17]

Future Directions

Indian Council of Medical Research-The National Centre for Disease Informatics and Research (ICMR-NCDIR) has established a population-based as well as a hospital-based stroke registry which is ongoing. To bridge the gap between demand and supply, earmarking thrombectomy-capable centers with stroke-ready teams, extensive training and retraining of healthcare workers on identification and prompt triage of LVO strokes, and ensuring hassle-free referral to stroke-ready centers in minimum possible time to reduce the onset to door time are some of the strategies which may help India march forward in providing the standard of care to MT-eligible patients. Awareness programs regarding stroke and management of stroke may change the misconceptions and perception of stroke in the society. COVID-19 pandemic has facilitated teleconsultations worldwide paving way for Telestroke programs which may be implemented in a spoke–hub model countrywide to bolster and guide time-sensitive stroke management in remote areas which are distant from stroke-ready centers. Manufacturing cost-effective devices and instruments, and ordering in bulk as stroke kits are feasible options to bring down the expenses of the procedure. Stringent policy-making to make stroke care affordable, ensuring reimbursement policies, and health insurance and government schemes to cover these lifesaving procedures are welcome steps. For India to realize its demographic dividend, we must preserve health, especially in the realm of stroke and its consequences.

Conclusion

MT is a revolutionary treatment modality which has changed the paradigm of acute stroke management, limiting stroke mortality and morbidity. Despite the obvious disparity in access of MT globally, India has marched forward albeit with small but steady steps. The barriers need to be addressed individually to strengthen policymaking and streamline affordable stroke care for all.

References

1. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke 2022;17(1):18–29. Erratum in: Int J Stroke 2022;17(4):478
2. Gerstl JVE, Blitz SE, Qu QR, et al. Global, regional, and national economic consequences of stroke. Stroke 2023;54(9):2380–2389
3. Rennert RC, Wali AR, Steinberg JA, et al. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. Neurosurgery 2019;85(suppl_1):S4–S8
4. Jones SP, Baqai K, Clegg A, et al. Stroke in India: a systematic review of the incidence, prevalence, and case fatality. Int J Stroke 2022;17(2):132–140
5. Sylaja PN, Pandian JD, Kaul S, et al. Ischemic stroke profile, risk factors, and outcomes in India: the Indo-US Collaborative Stroke Project. Stroke 2018;49(1):219–222
6. Abraham SV, Krishnan SV, Thaha F, Balakrishnan JM, Thomas T, Palatty BU. Factors delaying management of acute stroke: an Indian scenario. Int J Crit Illn Inj Sci 2017;7(4):224–230
7. Sundar K, Panwar A, Yagaval DR, Huded V, Sylaja PN. Mission Thrombectomy 2020 (MT2020)—India's biggest healthcare challenge yet. J Stroke Med 2020;3(2):62–71
8. Asif KS, Otite FO, Desai SM, et al; Global Executive Committee of the MT-GLASS Study. Mechanical Thrombectomy Global Access for Stroke (MT-GLASS): A Mission Thrombectomy (MT-2020 Plus) Study. Circulation 2023;147(16):1208–1220 Erratum in: Circulation 2023;147(16):e716

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9. Vibha D, Misra S, Desai SM, Prasad K, Srivastava AK, Pandit AK, Jadhav AP. Endovascular Thrombectomy Eligibility in the 0-24-Hour Time Window at a Large Academic Center in India. Neurol India. 2022 Mar-Apr;70(2):606-611
10. Das K, Mondal GP, Dutta AK, Mukherjee B, Mukherjee BB. Awareness of warning symptoms and risk factors of stroke in the general population and in survivors stroke. J Clin Neurosci 2007;14(1):12–16
11. Martins SO, Mont'Alverne F, Rebello LC, et al; RESILIENT Investigators. Thrombectomy for stroke in the public health care system of Brazil. N Engl J Med 2020;382(24):2316–2326
12. Mechanical Thrombectomy Devices for Acute Ischaemic Stroke. Nice.org.uk. Published 2018. Accessed March 11, 2020 at: https://www.nice.org.uk/advice/mib153/resources/mechanical-thrombectomy-devices-foracute-ischaemic-stroke-pdf-2285963514951109
13. India Climate & Energy Dashboard. NITI Aayog. https://iced.niti.gov.in/economy-and-demography/key-economic-indicators/socio-economic
14. Kulkarni P. The age at which you should get health insurance and the cover size you will need [online]. The Economic Times. Last updated: September 16, 2019. Accessed March 11, 2020 at: https://economictimes.indiatimes.com/wealth/insure/health-insurance/the-age-at-which-you-shouldget-health-insurance-and-the-cover-size-you-will-need/articleshow/71124561.cms?from=mdr
15. Pizzo E, Dumba M, Lobotesis K. Cost-utility analysis of mechanical thrombectomy between 6 and 24 hours in acute ischemic stroke. Int J Stroke 2020;15(1):75–84
16. Atchaneeyasakul K, Jadhav AP, Desai SM. Methods and apparatus for restoring flow US11291463B2 United States Patent And Trademarks Office 2022-04-05
17. Gravity Stent-Retriever System for Reperfusion of Large Vessel Occlusion Stroke Trial (GRASSROOT). ClinicalTrials.gov identifier: NCT06249776. Updated February 24, 2023. Accessed August 14, 2024 at: https://clinicaltrials.gov/study/NCT06249776

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10 Vagal Nerve Stimulation (VNS) versus Deep Brain Stimulation (DBS) for Intractable Epilepsy

Aditya Gupta, Pawan Goyal, and Sanjeev Srivastava

Introduction

Epilepsy as we all know is a very prevalent problem with 0.5 to 1% of the world's population suffering from one or the other forms of epilepsy.[1] A significant physical, financial as well as psychological burden is imposed not only on the patients but also on their families.

Antiepileptic drugs are the first line of management for these individuals. However, still close to one-third of the patients experience seizures despite on medications.[2] In most patients with medically refractory epilepsy, the quality of life, education, and livelihood opportunities are all impacted adversely.

Surgery is the second line of treatment for cases of drug-resistant epilepsy. The optimal indications for resective or disconnective surgery are well known. Patients with temporal lobe epilepsy, identifiable focal pathology such as hippocampal sclerosis or dysembryoplastic neuroepithelial tumor (DNET) on MRI, and well-localized epileptiform discharges on ictal video-electroencephalographic recordings are good candidates for surgery. A large majority of such patients have good outcomes from surgery, and this has been proven in some randomized trials as well.[3,4]

However, there still remains a significant group of intractable epilepsy patients who are not good candidates for resective or disconnective procedures owing to the seizure foci being multifocal and bilateral, eloquent or generalized. These are typically the "worst of the worst" cases encountered in an epilepsy clinic.

One of the most impressive achievements in epilepsy treatment over the past few decades is the progress in neurostimulation therapy. This is a new ray of hope for patients with drug-resistant epilepsy, for whom no surgical options existed.

The history of human brain stimulation for epilepsy dates back to 1886 when Sir Victor Horsley first utilized it for electrical cortical stimulation for mapping in a patient with focal epilepsy.[5]

Penfield and Wilder further published their work on cortical stimulation in 1954 and ushered in a golden age of cortical mapping and animal neuroscience studies.[6]

The use of neural stimulation has been encouraged by its increasing application to movement disorders. A variety of targets can be stimulated for epilepsy like the cerebellum, caudate nucleus, hippocampus, thalamus (including the centromedian, anterior and subthalamic nuclei), vagus nerve, and the epileptic focus itself.[7]

Brain stimulation devices provide a therapeutic option for people with drug resistant epilepsy (DRE), and essentially fill a gap for patients where the seizure-onset zone is multifocal, nonresectable, or poorly localized or if the patient is unwilling for a traditional epilepsy craniotomy procedure.

Presently, a number of implantable neurostimulation devices are in use for epilepsy

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treatment. Vagal nerve stimulation (VNS) and responsive neurostimulation (RNS) system have gained U.S. Food and Drug Administration (FDA) approval for the treatment of epilepsy, and deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT) has approval from the FDA and European Medicinal Agency. These modalities have shown clear benefit and are therefore already in active clinical use. Other neurostimulation modalities, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are also under investigation and have shown encouraging results.

The current chapter focuses on discussing the clinical efficacy of DBS and VNS for epilepsy by way of comparing the results, side effects, and delineating the patient groups that may benefit most from each. Moreover, we will review their features, mechanisms of action, and efficacy data.

Deep Brain Stimulation

DBS is a neurostimulation procedure which is already well established for treating Parkinson's disease and other movement disorders. It involves implanting electrodes in specific subcortical structures of the brain and attaching these electrodes to an implanted pacemaker-like device or pulse generator. Through this device, electrical impulses are delivered to specific areas of the brain to achieve the desired response. The pulse generator is generally implanted in a subcutaneous pocket in the subclavicular region.

Mechanism of Action

DBS is an open loop neurostimulator that suppresses seizures by providing continuous periodic electrical stimulation.[8]

Although the procedure is called as deep brain stimulation, the stimulated neural structures are inactivated functionally through a complex procedure. Stimulation of subcortical structures at a high frequency replaces natural neural activity with time-locked spikes at the stimulation frequency.[9,10]

This leads to antidromic collision of natural spikes with stimulus-driven spikes evoked at high frequency.[11] This therefore results in a functional inhibition of the stimulated target. This mechanism possibly blocks the propagation of ictal activity.

So DBS does not act against the pathophysiology of any specific disorder. It only modulates the brain circuits at some specific stimulation parameters.[12]

A number of subcortical structures have been studied for neurostimulation producing epilepsy control such as ANT, centromedian thalamic nucleus (CM), subthalamic nucleus (STN), caudate nucleus, cerebellum, and hippocampus.[13]

The ANT has rich connections with limbic system through the fornix and mammillothalamic tract.[14] Other advantages with ANT are its bigger size and distance from vascular structures which make it a safe target. Due to these reasons, it is considered to be one of the most preferred targets for DBS for epilepsy.[15]

In fact, DBS received FDA approval in 2018 based on multicenter, double-blind, and randomized trial of ANT stimulation for localization-related epilepsy (the SANTE trial). A statistically significant median seizure reduction was seen at the end of a 3-month blinded period (40.4% in stimulated vs. 14.5% in controls).[8]

Long-term follow-up also showed sustained efficacy and safety in a treatment-resistant population. The median percent seizure reduction was of 41% from baseline at 1 year and 69% at 5 years. The responder rate (≥50% reduction in seizure frequency) also showed improvement over time, as it was 43% at 1 year and 68% at 5 years. In the 5 years of follow-up, 16% of the subjects were seizure-free for at least 6 months.[16]

In Papez circuit, the ANT is the primary relay nucleus. It receives afferent inputs from hippocampal subiculum via the fornix/

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mammillothalamic tract and has reciprocal connections with the cingulate and frontal cortex. This circuit of ANT is considered to be responsible for the propagation of seizure activity.[17]

Centromedian nucleus (CM) is considered to be another important target for DBS in epilepsy. Velasco and colleagues first performed CM stimulation in humans for drug-resistant epilepsy.[18] Patients with primary or secondary Lennox-Gastaut syndrome (LGS) and having absence and generalized seizures are best suited for CM stimulation. Close to 80% of such patients show a good response. However, it is not effective for the treatment of focal onset seizures with altered sensorium.

In a mixed cohort including four patients with LGS, with centromedian thalamic deep brain stimulation (CM-DBS), there was 68% mean seizure reduction along with seizure freedom rate of 9%. All four patients had a reduction in frequency of seizure by >50% (100% response rate).[19] There are some differences in indications and trajectory of these two targets.[20] Important features of difference in the two main targets are mentioned in **Table 10.1**.

Apart from these two targets, there are other target structures that have been investigated. Stimulation of cerebellum has had conflicting results over the past 50 years.[13]

About 25% of the patients were seizure-free and 50% were improved with cerebellar stimulation in uncontrolled trials. On the contrary, controlled studies showed no benefit in a small group of patients.[7]

Another important target for stimulation is hippocampus. It is indicated for patients with drug-resistant mesial temporal lobe epilepsy (MTLE), especially patients in whom surgery cannot be done. Seizure reduction was 15 to 33% and responder rates were 55% in three double-blind studies.[21–23]

STN stimulation is also used in drug-resistant epilepsy; however, its effect is still doubtful. There is a possible role of subthalamic inhibition in seizure control based on demonstration of nigral control by Gale in an epilepsy model.[24] However, the effect is not predictable and there are many variables such as type of seizures and preexisting brain damage which can influence the overall outcome.

Another target investigated for stimulation was the head of caudate nucleus (HCN). Low frequency electrical stimulation leads to inhibitory effect on epileptiform spikes from ipsilateral hippocampus and amygdala.[25]

Chkhenkeli et al stimulated the ventral HCN at low frequency (4–8 Hz) in 38 patients, producing seizure freedom in 21 patients, while improving 35 patients overall (92%).[26]

Technique

The DBS procedure for epilepsy involves three major steps. The initial step is a preoperative planning. It is the most important step as

Table 10.1 ANT-DBS versus CM-DBS

	ANT-DBS	CM-DBS
Seizure type	Focal to secondary generalized tonic-clonic seizures	Primary generalized tonic-clonic seizures with multiple epileptic foci
Location of epileptic foci	Mesial/temporal or frontal brain regions	Precentral motor areas, and primary somatosensory cortex
Patients with intellectual disability	Usually avoided	No contraindication
Standard trajectory	Transventricular	Transparenchymal extraventricular

Abbreviations: ANT-DBS, anterior nucleus of thalamus–deep brain stimulation; CM-DBS, centromedian nucleus–deep brain stimulation.

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the stereotactic coordinates of the desired target are calculated based on merging of preoperative MRI with a frame based (or frameless) imaging or atlas. The second step is the surgical procedure for implantation of DBS leads at the desired target. It can be done under local or general anesthesia. It involves a team of neurosurgeons, epileptologists, and technical device staff. Initially the exact target placement and trajectory are determined and then the burr hole is placed after frame setup and prepping of scalp (**Fig. 10.1**). Once the micro-electrodes are placed with the help of a microdrive, neuronal activity specific to the region in question is recorded and assessed by an epileptologist (**Fig. 10.2**). Intraoperative fluoroscopy or a CT is helpful in determining the exact placement of micro-electrode tip. Next, with the same micro-electrodes, stimulation is done to demonstrate the effect on neuronal activity. In the case of DBS for epilepsy, the indicative finding is that of a synchronizing "driving response" seen on the EEG electrodes typically at low frequency (approximately 5 Hz) stimulation. Once a satisfactory position is determined, the DBS electrode is inserted at the same point and micro-electrodes are withdrawn. At this point an intraoperative fluoroscopy may be quite helpful in confirming the accuracy of lead electrode placement. Next the lead is secured in place at burr hole with a special "base" and "cap" and the distal end of the lead is connected to connectors which are in turn tunneled to a subcutaneous pocket (generally below clavicle) which houses the implantable pulse generator (IPG). We generally take an O-arm intraoperative three-dimensional CT scan immediately postoperatively and merge it with the preoperative MRI to confirm lead tip position and to see the lead path and trajectory (**Fig. 10.3**). The third step is the postoperative assessment and this is performed by the epileptologist intraoperatively in OR and postoperatively in the ICU.

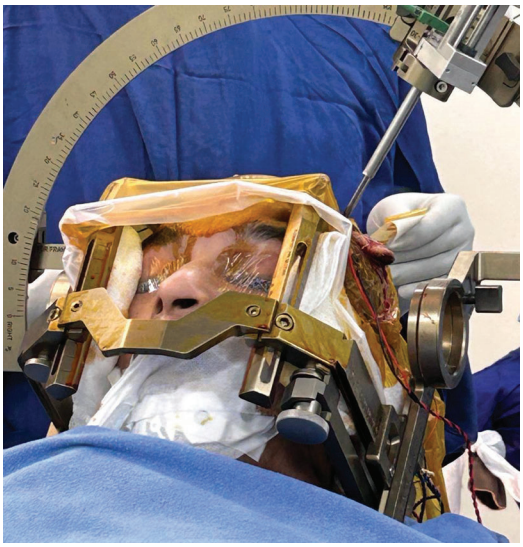

Fig. 10.1 Deep brain stimulation (DBS) surgery for epilepsy technique. Leksell frame applied on a patient.

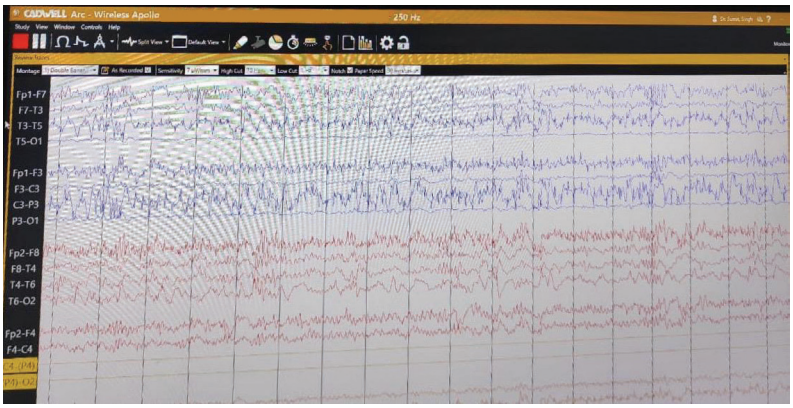

Fig. 10.2 Deep brain stimulation (DBS) surgery for epilepsy technique. Intraoperative EEG.

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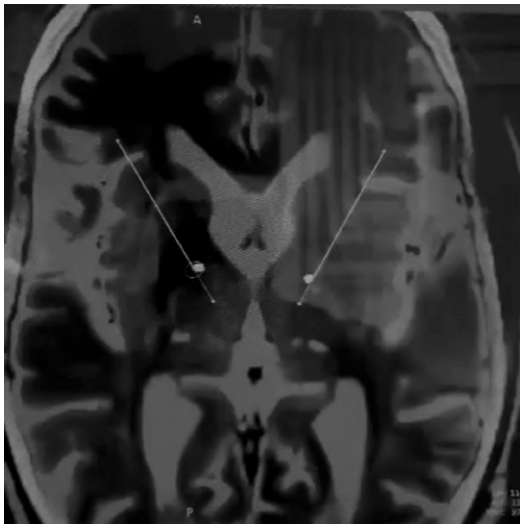

Fig. 10.3 Deep brain stimulation (DBS) surgery for epilepsy technique. Fusion of O-arm and preoperative MRI image to confirm accurate lead placement.

Vagus Nerve Stimulator

There have been several attempts to control seizures by electrical stimulation of central and peripheral nervous systems. The first attempts with VNS began in the 1980s and the first human vagus nerve stimulator was implanted in 1988. Since then, there have been a number of clinical trials which have proved its efficacy. It received FDA approval in 1997.[27]

The exact mechanism of action of VNS is not yet fully understood.[28] Initially, it was thought that VNS stimulates unmyelinated type C fibers and desynchronizes EEG through tractus solitarius and medullary reticular formation pathways which result in decreased excitatory and increased inhibitory neurotransmission.

However, with more research, it was found that vagal afferents project to diffuse areas of the central nervous system, many of which are potential sites of seizure genesis. These include the cerebellum, diencephalon, amygdala, hippocampus, insular cortex, and multiple brainstem centers.

Majority of these projections relay through the nucleus tractus solitarius, while a smaller proportion forms direct, monosynaptic connections with their targets in the medial reticular formation of the medulla, the dorsal motor nucleus of the vagus, the area postrema, and the nucleus cuneatus.[29,30]

It still remains unclear which of these pathways underlie the mechanism of VNS action. It is believed that locus coeruleus (LC) and dorsal raphe nucleus (DRN) are important substrates. Further, norepinephrine and serotonin, which are diffusely released by the LC and DRN, respectively, may influence the antiepileptic effects of VNS.[31]

These two neurotransmitters induce interneurons to release gamma-amino butyric acid (GABA) in some parts of the brain and modulate seizure threshold leading to widespread neuronal inhibition of excitability in the brain.

Over a period of time, seizure frequency decreases with VNS. According to McHugh classification, 50% responder rate is the decrease in frequency by ≥50%, i.e., classes 1 and 2.[32] In a large-scale study focusing on adult epilepsy, the 50% responder rate was 23% at 3 months, 37% at 1 year, and 44% at 2 years after starting stimulation which again emphasizes the fact that seizure frequency decreases over a period of time.[33]

Similar to the case in adults, VNS has also been found to be effective in childhood drug-resistant epilepsy. In an open-label multicenter study report of 347 children of age 6 months to 17.9 years, a 50% responder rate in the baseline seizure frequency of the predominant seizure type was found to be 32.5, 37.6, and 43.8% of the patients, respectively at 6, 12, and 24 months after implantation. A total of 19 patients (5.5%) were completely free from seizures.[34]

Apart from its effect on seizures, VNS also has been observed to lead to improved emotional stability and sociability, which results in positive outcomes for the child's development and quality of life (QoL).[35]

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The side effects related to VNS are reactive cough, change in voice, paresthesia, nausea, salivation, and pain in back of the head. These side effects are however reversible, settle over a period of time, and can be managed with change in stimulation settings. The only side effect of concern is wound infection. In a study of 808 patients, 12 (1.5%) patients had wound infection.[36]

Technique

Generally, the left side of the neck is preferred and under general anesthesia, a 3- to 4-cm incision is placed halfway between mastoid and clavicle (very similar to Cloward–anterior cervical diskectomy and fusion [ACDF] incision) and medial fascial aspect of sternocleidomastoid muscle and carotid sheath are identified. The vagus nerve is found nestled between the carotid artery and internal jugular vein. A 3- to 4-cm length is identified and loops of the electrodes are wrapped around the nerve. The distal end of the electrode is tunneled to a subclavicular pocket wherein an IPG is attached and anchored securely. The steps of surgery are demonstrated in **Figs. 10.4–10.13**. Stimulation is started generally after 2 weeks.

Fig. 10.4 Vagal nerve stimulation (VNS) surgery technique. Skin incision for VNS implantation.

Fig. 10.5 Vagal nerve stimulation (VNS) surgery technique. Exposure of soft tissues and carotid sheath.

Fig. 10.6 Vagal nerve stimulation (VNS) surgery technique. Identification of left vagus nerve.

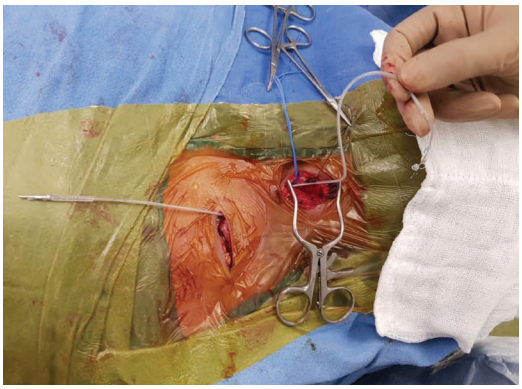

Fig. 10.7 Vagal nerve stimulation (VNS) surgery technique. Tunneling of electrode.

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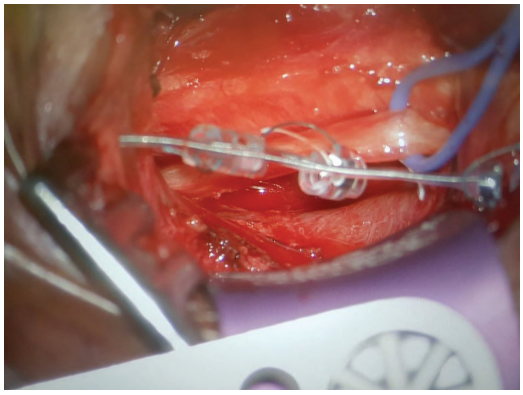

Fig. 10.8 Vagal nerve stimulation (VNS) surgery technique. Bringing of electrode loops near the vagus nerve.

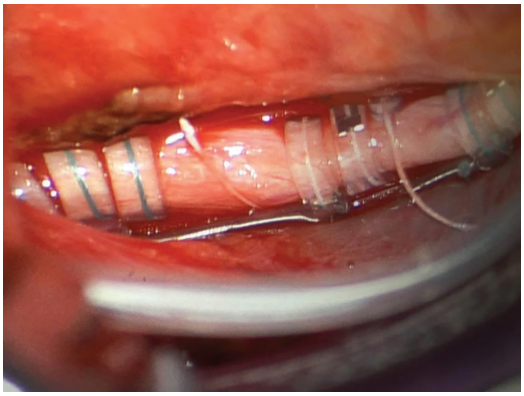

Fig. 10.9 Vagal nerve stimulation (VNS) surgery technique. Placement of electrode loops on the vagus nerve.

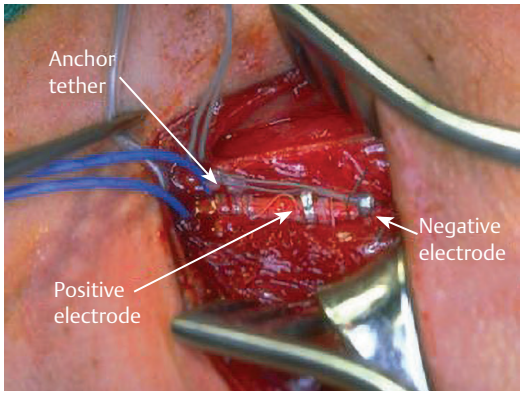

Fig. 10.10 Vagal nerve stimulation (VNS) surgery technique. Placement of electrode loops on the vagus nerve and anchors.

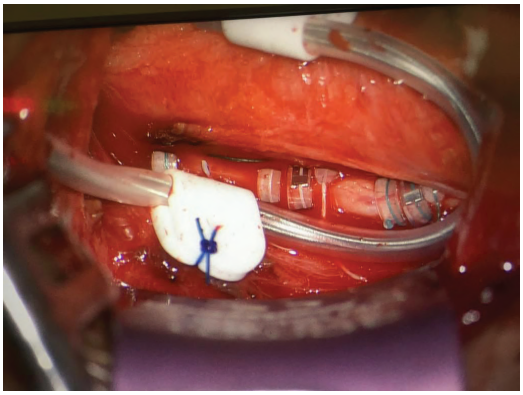

Fig. 10.11 Vagal nerve stimulation (VNS) surgery technique. Placement of silastic anchors for strain relief loops.

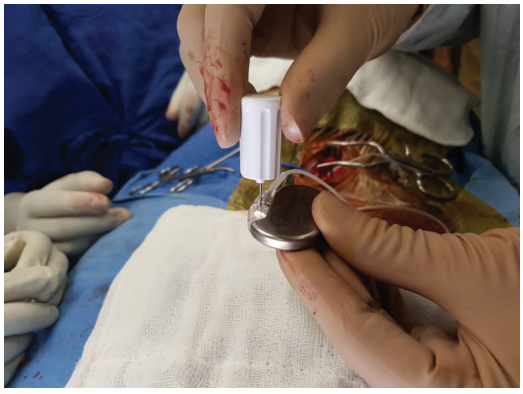

Fig. 10.12 Vagal nerve stimulation (VNS) surgery technique. Connection to implantable pulse generator.

Fig. 10.13 Vagal nerve stimulation (VNS) surgery technique. Surgical wound after the procedure.

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DBS versus VNS

Mechanism of Action

VNS is a less invasive device compared to DBS, but the efficacy may be more limited. VNS acts via its widespread influence on CNS noradrenergic projections.

DBS in epilepsy works on the principle similar to that for movement disorders: potential cellular inhibition or excitation (neuromodulation) directly and more specifically within the target structure.[37]

Outcome

In a single-center retrospective analysis of 35 patients by Zhu et al,[38] comparative study on the effectiveness of the two methods was done. Out of a total 35 patients with drug-resistant epilepsy, 17 patients underwent VNS therapy and 18 patients underwent DBS. The study duration was for 1 year after surgery. The linear regression analysis was applied on the age of onset, duration of epilepsy, numbers of antiepileptic drugs (AEDs), and the seizure reduction at 12 months after operation. The mean seizure reduction in patients with VNS at 3, 6, 9, and 12 months after the operation was 36.06, 39.94, 45.24, and 48.35%, while with DBS it was 57.22, 61.61, 63.94, and 65.28%, respectively. At 1 year after the operation, the patients with focal generalized seizures, history of craniotomy, and longer duration of disease responded better to DBS. Patients with focal seizures and older age of onset responded better to VNS. Overall, the efficiency of ANT-DBS was higher than that of VNS at each follow-up time point.

In a review of pivotal trials by Wong et al,[39] efficacy of DBS, RNS, and VNS were compared. It was found that efficacy of all devices improves over time possibly due to neuromodulatory effects and due to gradual change in the epileptic network in addition to any acute seizure-abortive effects. DBS appears to continue to increase in efficacy for many years while VNS results are variable. Overall, the efficacy of VNS is less as compared to DBS. One possibility can be the "microlesioning" effect of electrodes disrupting epileptic network, which is seen in DBS, while that effect cannot be expected in VNS.

In another meta-analysis by Skrehot et al,[40] seizure reduction efficacy of DBS, RNS, and VNS for focal epilepsy was compared. Seizure reduction for the devices at years 1, 2, and 3 respectively were: RNS: 66.3, 56.0, and 68.4%; DBS: 58.4, 57.5, and 63.8%; VNS: 32.9, 44.4, and 53.5%. Seizure reduction at year 1 was greater for RNS ($p < 0.01$) and DBS ($p < 0.01$) compared to VNS.

In a study by Park et al,[41] ANT-DBS was done on failed VNS cases for refractory epilepsy. Out of 7 patients, 5 (71.3%) experienced a >50% reduction of seizure counts after DBS; 1 responder reached a seizure-free status after DBS therapy. Of the two nonresponders, one subject showed improvement in seizure strength and duration, which lessened the impact of the seizures on the patient's quality of life. Focal impaired awareness seizures (FIAS), focal to bilateral tonic-clonic (FBTC) seizures, showed a trend to respond better to DBS than did other types of seizures. The results show that DBS could be considered as a further treatment option for refractory epilepsy patients even if they have previously experienced VNS failure.

Although Benbadis et al[42] in their study had compared the three available options VNS, RNS, and DBS for intractable epilepsy, here we are only comparing DBS and VNS head-to-head. DBS, like VNS, does not require localization and is therefore an option for unlocalizable or multifocal epilepsy. The evidence for DBS in generalized epilepsies is limited.[43,44]

DBS and VNS are palliative with a relatively low long-term seizure-free outcome. They are a secondary choice after a resective surgery is deemed not possible. As mentioned, DBS seems to have a higher efficacy compared to VNS[38–41] although other authors feel that both

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are generally comparable in terms of efficacy in various trials and also over long-term follow-up.[43–46]

DBS is more invasive than VNS and it is logical that less invasive methods should be preferred, and this may indeed be the reason for higher popularity of VNS in pediatric patients. DBS and older VNS models are open-loop systems, while newer VNS models are closed-loop systems (brain-responsive and heart-responsive respectively). The closed-loop systems are "smarter" or more elegant, but whether they result in superior efficacy to patients is not clear.

DBS and VNS are appropriate for focal epilepsies that are nonlocalizable or multifocal, in addition to well-defined focal epilepsies, but though DBS may be more efficacious, it is more invasive (intracranial), and VNS could be tried first, as currently recommended in Europe. DBS and VNS both have also been tried for generalized epilepsies, though that may be off-label depending on the country or continent, but this is less clear for DBS. In general, neurostimulation efficacy does not decrease over time, and may in fact increase, which is a significant advantage over medications. VNS has no typical systemic side effects of AEDs, and may reduce the risk of sudden unexplained death in epilepsy (SUDEP).[45–48]

VNS is the least "invasive," is useful for generalized or multifocal or unlocalizable epilepsies, and can also be used in children (e.g., FDA indication is down to 4 years).

Shah et al[49] have also compared the three modalities of neurostimulation and found more than 50% reduction of frequency of seizures over a period of 5 years. VNS scored better on relief from neuropsychological effects like word recognition, improvement in verbal concentration, and independent effect on mood.

In 2010, Fisher et al also noted a higher response rate of DBS over VNS, especially in patients with previous epilepsy surgery or an already implanted VNS, but the difference was not statistically significant. Furthermore, the risk of complications like death (SUDEP), infection, hemorrhage, and status epileptics was more, but again not statistically significant.[8]

Economic Comparison

Chan et al compared cost effectiveness of DBS and VNS and usual care of patients with refractory epilepsy. When compared with care as usual (CAU), incremental cost-effectiveness ratios (ICERs) showed that costs per quality-of-life years (QALYs) gained were slightly lower for DBS (€46,640) than for VNS (€47,155).[50]

Conclusion

Both DBS and VNS are well-established procedures for drug-resistant intractable epilepsy with almost comparable benefits as far as reduction in seizure frequency and seizure freedom is concerned. DBS scores better over a long-term follow-up but VNS is less invasive, technically easier, useful even in children, and has less complication rates as compared to DBS. With the newer "closed-loop" systems, VNS is gaining popularity. Although DBS is widely available, VNS is rather an underutilized technology especially in the developing world where it has to be made more available. Given that the cost of DBS and VNS procedures are very similar, in the Indian scenario using a more efficacious option (DBS) may be preferable. Cost and affordability still remain a big challenge in this part of the world, so we may not always have the luxury of first trying a lesser invasive option and then going to the other.

References

1. Theodore WH. Brain stimulation for epilepsy. Nat Clin Pract Neurol 2005;1(2):64–65
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314–319
3. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized,

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controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345(5):311–318
4. Engel J Jr, McDermott MP, Wiebe S, et al; Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 2012;307(9):922–930
5. Vilensky JA, Gilman S. Horsley was the first to use electrical stimulation of the human cerebral cortex intraoperatively. Surg Neurol 2002;58(6):425–426
6. Penfield WJHH, Wilder P, Epilepsy, Cerebral l. Epilepsy and the Functional Anatomy of the Human Brain. 1st Boston: Little, Brown; 1954. xv, 896
7. Theodore WH, Fisher RS. Brain stimulation for epilepsy. Lancet Neurol 2004;3(2):111–118; erratum Lancet Neurol 3: 332
8. Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899–908
9. Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosci 2003;23(25):8743–8751
10. Garcia L, D'Alessandro G, Fernagut PO, Bioulac B, Hammond C. Impact of high-frequency stimulation parameters on the pattern of discharge of subthalamic neurons. J Neurophysiol 2005;94(6): 3662–3669
11. Griffin DM, Hudson HM, Belhaj-Saïf A, Cheney PD. Hijacking cortical motor output with repetitive microstimulation. J Neurosci 2011; 31(37):13088–13096
12. DeLong M, Wichmann T. Deep brain stimulation for movement and other neurologic disorders. Ann N Y Acad Sci 2012;1265:1–8
13. Lin Y, Wang Y. Neurostimulation as a promising epilepsy therapy. Epilepsia Open 2017;2(4): 371–387
14. Kotagal P. Neurostimulation: vagus nerve stimulation and beyond. Semin Pediatr Neurol 2011; 18(3):186–194
15. Wu C, Sharan AD. Neurostimulation for the treatment of epilepsy: a review of current surgical interventions. Neuromodulation 2013;16(1): 10–24, discussion 24
16. Salanova V, Witt T, Worth R, et al; SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84(10):1017–1025
17. Oikawa H, Sasaki M, Tamakawa Y, Kamei A. The circuit of Papez in mesial temporal sclerosis: MRI. Neuroradiology 2001;43(3):205–210
18. Velasco F, Velasco M, Jiménez F, et al. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 2000;47(2):295–304, discussion 304–305
19. Son B-C, Shon YM, Choi J-G, et al. Clinical outcome of patients with deep brain stimulation of the centromedian thalamic nucleus for refractory epilepsy and location of the active contacts. Stereotact Funct Neurosurg 2016;94(3):187–197
20. Sobstyl M, Konopko M, Wierzbicka A, Prokopienko M, Pietras T, Sipowicz K. Deep brain stimulation of anterior nucleus and centromedian nucleus of thalamus in treatment for drug-resistant epilepsy. Neurol Neurochir Pol 2024;58(3):256–273
21. Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 2006;66(10):1490–1494
22. Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 2007;48(10):1895–1903
23. McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia 2010; 51(2):304–307
24. Deransart C, Lê BT, Marescaux C, Depaulis A. Role of the subthalamo-nigral input in the control of amygdala-kindled seizures in the rat. Brain Res 1998;807(1-2):78–83
25. Ge Y, Hu W, Liu C, Zhang JG, Meng FG. Brain stimulation for treatment of refractory epilepsy. Chin Med J (Engl) 2013;126(17):3364–3370
26. Chkhenkeli SA, Sramka M, Lortkipanidze GS, et al. Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 2004;106(4):318–329
27. Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 1990; 31(Suppl 2):S40–S43
28. Amar AP, Heck CN, Levy ML, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy:

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rationale, technique, and outcome. Neurosurgery 1998;43(6):1265–1276, discussion 1276–1280
29. Rutecki P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 1990;31(Suppl 2): S1–S6
30. Cheng G, Zhou X, Qu J, Ashwell KW, Paxinos G. Central vagal sensory and motor connections: human embryonic and fetal development. Auton Neurosci 2004;114(1-2):83–96
31. Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. J Pharmacol Exp Ther 2006;318(2): 890–898
32. McHugh JC, Singh HW, Phillips J, Murphy K, Doherty CP, Delanty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 2007;48(2):375–378
33. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 2002; 1(8):477–482
34. Orosz I, McCormick D, Zamponi N, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 2014;55(10):1576–1584
35. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia 2014;55(6): 893–900
36. Hasegawa H, Van Gompel JJ, Marsh WR, et al. Outcomes following surgical management of vagus nerve stimulator-related infection: a retrospective multi-institutional study. J Neurosurg 2020; 135(3):783–791
37. Hamani C, Hodaie M, Lozano AM. Present and future of deep brain stimulation for refractory epilepsy. Acta Neurochir (Wien) 2005;147(3):227–229
38. Zhu J, Wang X, Xu C, et al. Comparison of efficiency between VNS and ANT-DBS therapy in drug-resistant epilepsy: a one year follow up study. J Clin Neurosci 2021;90:112–117
39. Wong S, Mani R, Danish S. Comparison and selection of current implantable anti-epileptic devices. Neurotherapeutics 2019;16(2):369–380
40. Skrehot HC, Englot DJ, Haneef Z. Neuro-stimulation in focal epilepsy: a systematic review and meta-analysis. Epilepsy Behav 2023;142:109182
41. Park HR, Choi SJ, Joo EY, et al. The role of anterior thalamic deep brain stimulation as an alternative therapy in patients with previously failed vagus nerve stimulation for refractory epilepsy. Stereotact Funct Neurosurg 2019;97(3):176–182
42. Benbadis SR, Geller E, Ryvlin P, et al. Putting it all together: options for intractable epilepsy: an updated algorithm on the use of epilepsy surgery and neurostimulation. Epilepsy Behav 2018;88S:33–38
43. Salanova V. Deep brain stimulation for epilepsy. Epilepsy Behav 2018;88S:21–24
44. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia 2018;59(2):273–290
45. Geller EB. Responsive neurostimulation: review of clinical trials and insights into focal epilepsy. Epilepsy Behav 2018;88S:11–20
46. Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy Behav 2018;88S:2–10
47. Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018;59(3):562–572
48. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia 2018;59(3):555–561
49. Shah V, Eliashiv D, Demer M, et al. Neurostimulation & epilepsy. Epilepsy 2019:68–71
50. Chan HY, Wijnen BFM, Majoie MHJM, Evers SMAA, Hiligsmann M. Economic evaluation of deep brain stimulation compared with vagus nerve stimulation and usual care for patients with refractory epilepsy: a lifetime decision analytic model. Epilepsia 2022;63(3):641–651

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11 Tuberculum Sellae Meningioma: Transcranial Microsurgical Excision

Sunil Kumar Gupta, Sushant Kumar Sahoo, Apinderpreet Singh, and Sandeep Mohindra

Anatomy

Tuberculum sella is a part of skull base that separates the planum sphenoidale anteriorly and sella turcica posteriorly. Posteriorly, planum sphenoidale terminates as limbus sphenoidale. Between the limbus and the tuberculum sellae lies the chiasmatic sulcus also called as optic groove (**Fig. 11.1**). Meningioma usually arises from the dorsal surface of the tuberculum sellae close to the optic canal.[1] Tuberculum sellae is closely associated with the optic apparatus. The optic chiasm is anatomically located just superior and posterior in relation to the chiasmatic sulcus. On the lateral end of the tuberculum sellae, optic nerve enters the optic canal on both sides.

The cavernous segment of internal carotid artery (ICA) turns laterally to become the clinoidal segment in close relation to the optic nerve. The cavernous and clinoidal segment of ICA runs inferior and lateral to the optic canal. At this point superior hypophyseal artery, a branch of ICA, turns medially to supply the optic chiasm. The A1 segment of anterior cerebral artery lies superior to the tuberculum sellae and is often pushed superolaterally by tuberculum sellae meningioma (**Fig. 11.2**). The Acom complex along with the proximal A2 lies in the chiasmatic cistern, anterior and superior to the optic chiasm.

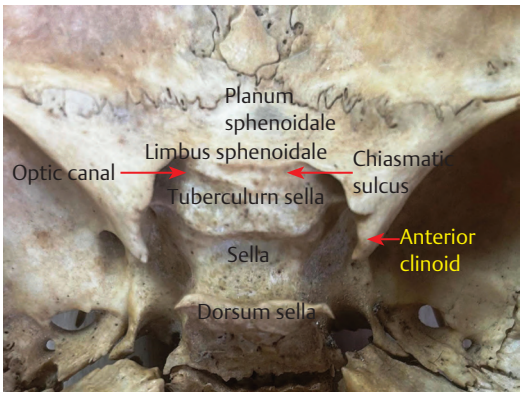

Fig. 11.1 Image showing important bony structures in relation to tuberculum sella.

Origin of Tuberculum Sellae Meningioma and Its Relation with Neurovascular Structures

Tuberculum sellae meningioma constitutes approximately 5 to 10% of all intracranial meningiomas and can arise from anywhere along the dura over tuberculum sellae, chiasmatic sulcus, or limbus sphenoidale.[1,2] Anatomically, it can be central, paracentral/unilateral, or large enough to involve the entire tuberculum sellae and may involve the optic strut and anterior clinoid process. As these tumors grow in size, they are bounded superolaterally by the optic nerve, posteriorly by optic chiasm, and inferolaterally by the cavernous and clinoidal ICA (**Fig. 11.2**). In large tumors the A1–Acom complex may get pushed superiorly and posteriorly, and at times may get engulfed/encased by the tumor (**Fig. 11.3**).

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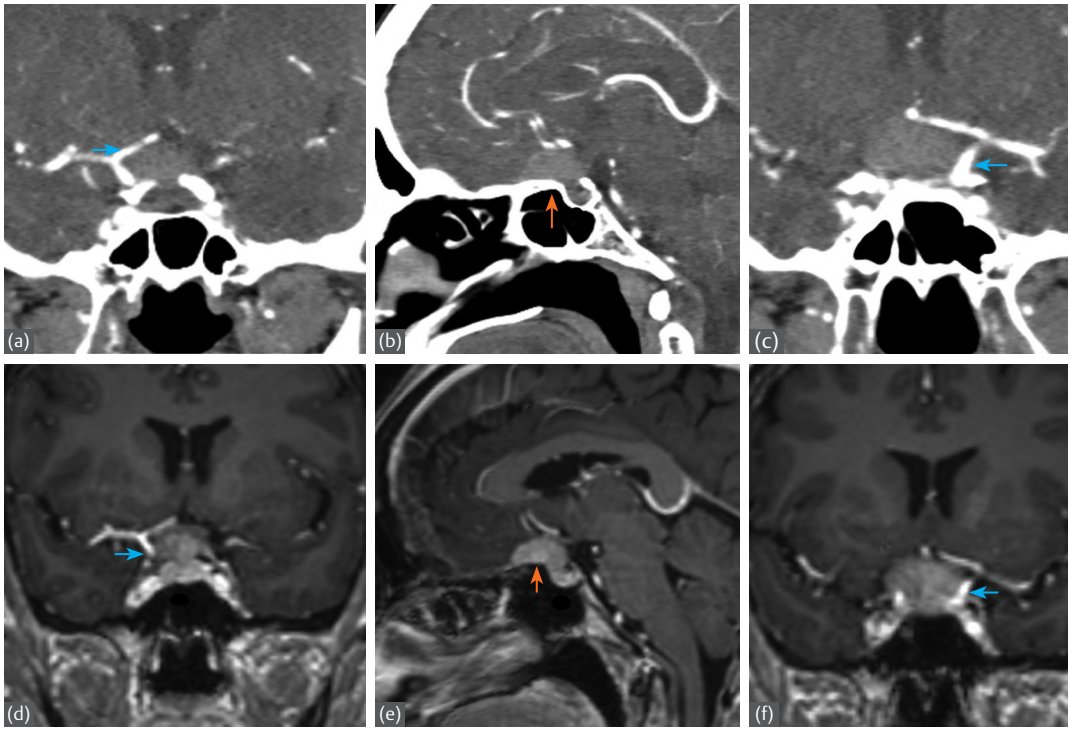

Fig. 11.2 Radiology showing CT angiography (upper row, **a–c**) and contrast MRI (lower row, **d–f**) of brain with tuberculum sella meningioma. The epicenter of meningioma is noted at the tuberculum sella (orange arrow on **b**, **e**). Note the lateral displacement of the cavernous internal carotid artery (ICA) by the meningioma (blue arrow on **c**, **d**, **f**). The A1 is pushed superolaterally (blue arrow on **a**) by the tumor.

The proximity of these tumors with the optic apparatus explains early presentation of visual deficit in these patients. Visual deficit can present in up to 80% of patients with tuberculum sellae meningiomas.[2–4] The patterns of loss of vision directly correspond with the tumor location. Central tumors with compression over the optic chiasm may produce bilateral temporal (superior quadrant) field defect whereas unilateral visual field defects may be noticed with off-midline location of meningioma close to the optic canal and the optic nerve. In approximately 67% of cases, tuberculum sellae meningioma may invade the optic canal.[5] Meningiomas arising from the dura over tuberculum sellae, planum sphenoidale, diaphragm sella, and anterior clinoid process are called as suprasellar meningiomas and are often difficult to differentiate. Usually, meningioma arising from the tuberculum sellae tends to push the optic chiasm and nerve upwards while those arising from the planum push the optic apparatus downward and backward.[2]

Imaging and Investigations

Contrast-enhanced magnetic resonance imaging (CEMRI) is the preferred radiological investigation. CEMRI must be evaluated carefully to localize the lesion, dural tail, invasion into the optic canal, encasement of adjacent vessels, position of the pituitary stalk etc. (**Figs. 11.2** and **11.3**). Heavily weighed T2 MRI may provide important information of the optic nerve and optic chiasm in relation to the meningioma. Computed tomography (CT) images provide additional information like

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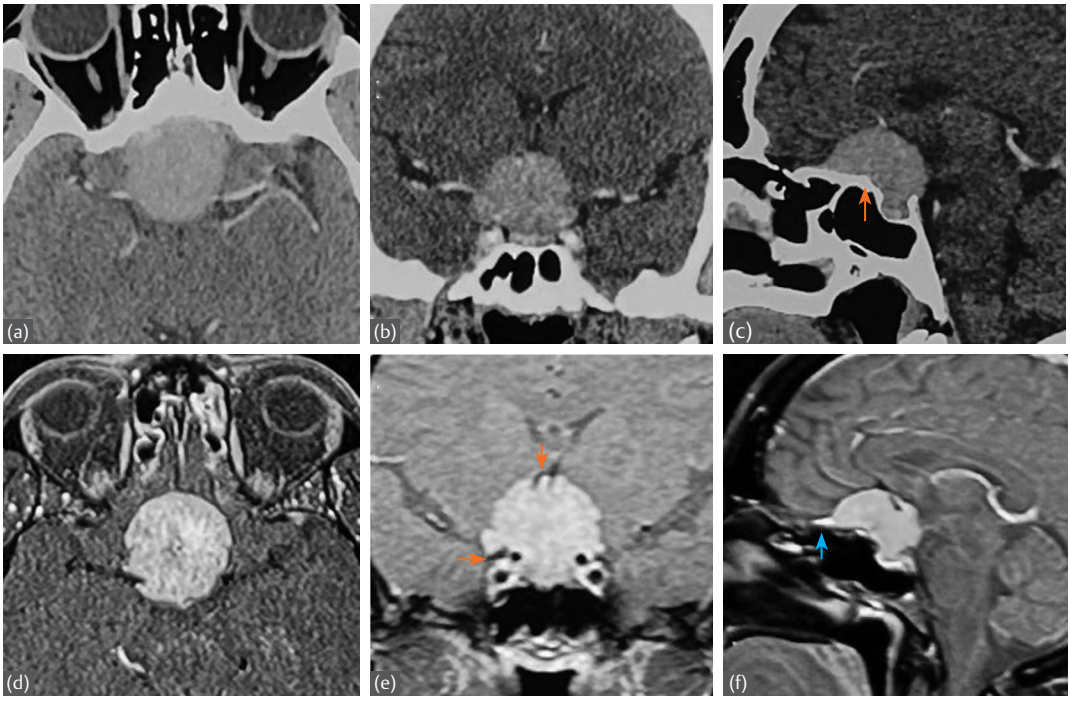

Fig. 11.3 Image showing tuberculum sella meningioma on non contrast computed tomogram (NCCT) imaging (upper row, **a–c**) and contrast MR imaging (lower row, **d–f**). The epicenter of tumor is located on tuberculum sella (orange arrow, 3c) and dural tail extending to anterior skull base (blue arrow, 3f). Note the tumor encasing bilateral cavernous internal carotid artery (ICA) and A2 (orange arrows, 3e).

hyperostosis of adjacent bony structures and presence of any intratumoral calcification. CT angiography further provides information on peritumoral arteries.

In standard practice CEMRI, CT, and CT angiography are considered essential for planning surgery in all cases of tuberculum sellae meningioma.

Considering the high incidence (60 to 90%) of visual impairment in tuberculum sellae meningioma, complete visual assessment must be done in the preoperative period.[2] Combined assessment of visual acuity (using Snellen chart) and visual field (using standard Goldman perimetry technique) is important. Visual impairment score can be calculated after combining the impairment in visual acuity and field as suggested by the German Ophthalmological Society. The score ranges from 0 to 100 where higher the score more is the visual deficit.[6]

Fundoscopy and optical coherence tomography can be utilized further to assess the functional status of visual pathway. However, visual acuity and visual field are commonly used in the preoperative and postoperative periods (at 3 months follow-up) to assess the improvement in vision following surgery.

Preoperative hormonal deficits have been reported in up to 40% of patients. Although anterior pituitary hormone deficiency is noted in 8.4% of patients after surgery, postoperative diabetes insipidus may be detected in 3 to 26% of patients.[2] Therefore, complete hormonal evaluation must be a part of preoperative and postoperative management in these patients.

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Surgery

Tuberculum sellae meningiomas can be operated through transcranial or extended endoscopic endonasal approaches. The corridor in transcranial approach may vary depending on the extension of tumor and surgeon's choice. Commonly considered transcranial approaches for tuberculum sellae meningioma use the transsylvian and/or subfrontal corridor. Accordingly, pterional/frontotemporal craniotomy, subfrontal and lateral subfrontal approach, orbitofrontal craniotomy, bifrontal craniotomy and basal anterior interhemispheric approach, and supraorbital key hole craniotomy have been described in the literature.

Anterior interhemispheric approaches provide a direct access to the tumor and its posterosuperior extension and a symmetrical view of both the optic nerves and carotid vessels as well as the anterior communication artery complex. However, it entails some retraction of both frontal lobes and necessitates sectioning of the anterior superior sagittal sinus. In addition, there are more chances of impaired olfaction with this approach. The subfrontal approach provides a direct access to the tumor, but some degree of frontal lobe retraction is unavoidable. In addition, a large frontal sinus can be troublesome. Anterolateral approaches, such as pterional craniotomy and its variants, provide the shortest route to the tumor with the advantage of both a subfrontal and transsylvian access. This route also obviates the risk of frontal sinus opening in most patients. A careful interfascial or subfascial dissection must be done to avoid injury to branches of the facial nerve. Opening of the sylvian fissure and cerebrospinal fluid (CSF) release can minimize or obviate the need of frontal lobe retraction. In cases where the tumor attachment is eccentric, the ipsilateral optic nerve gets stretched and may need to be mobilized to access the tumor base. In such cases, a contralateral approach may be preferred to decompress the tumor and reduce optic nerve manipulation. In all transcranial approaches, the basic steps of surgery almost remain the same. Occasionally tumor may extend into the optic foramen, demanding drilling of the optic strut and anterior clinoid process. The drilling of the anterior clinoid process, if needed, can be done either intradural or extradural. Clinoidectomy, in addition to decompression of the optic nerve, also results in significant devascularization of the tumor (**Fig. 11.4**).

Devascularization of Tumor

Once the tumor is reached it is important to define the tumor and identify the attachment with skull base dura (**Fig. 11.5**). Devascularization of the meningioma can be performed by coagulating the base of the

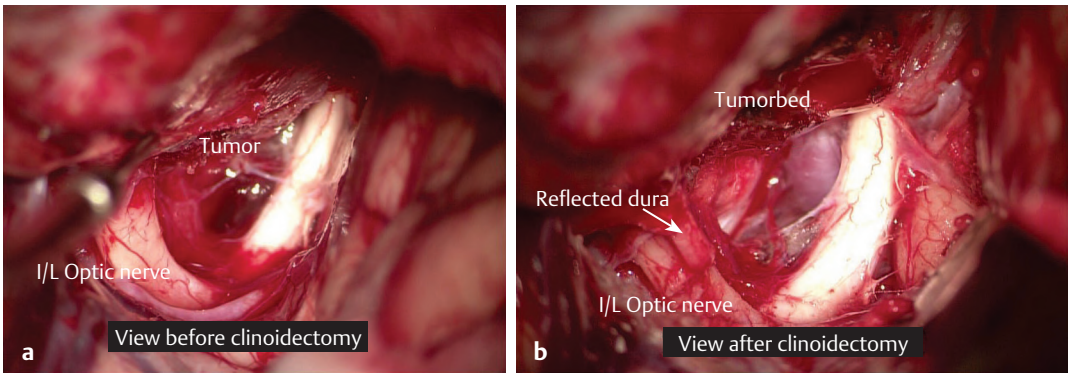

Fig. 11.4 **(a)** Intraoperative image showing a displaced optic nerve before clinoidectomy **(b)** and view after partial clinoidectomy and removal of tumor extension into the optic canal.

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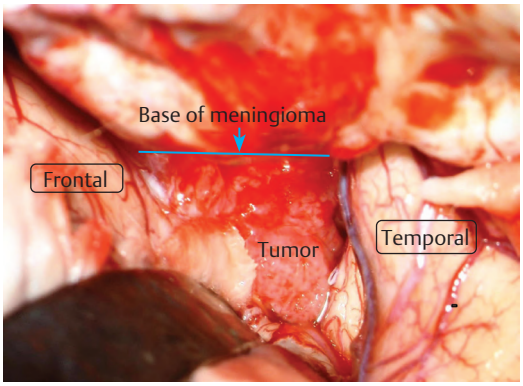

Fig. 11.5 Intraoperative image showing the base of meningioma.

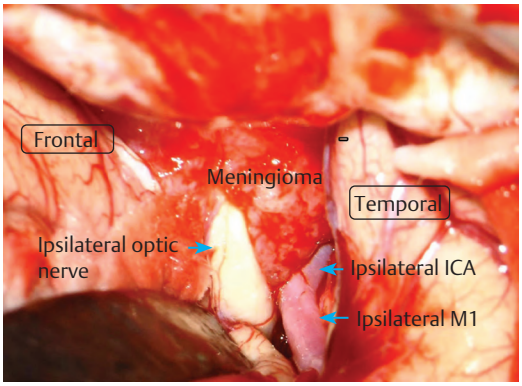

Fig. 11.6 Intraoperative image showing the ipsilateral optic nerve, internal carotid artery (ICA), and M1 in relation to the tumor.

tumor and cutting the blood supply from the dura over tuberculum sellae. Important neurovascular structures like ipsilateral ICA, ipsilateral/contralateral optic nerve, and ipsilateral A1 need to be delineated before starting further dissection.

Decompression of Optic Nerve

Majority of the meningiomas grow laterally and push/compress the optic nerve. It is important to sharply dissect the tumor from the optic nerve first. Minor manipulation or stretching of the nerve may compromise its function and the patient may have postoperative visual deficit. If the nerve is compressed, thinned and stretched over the tumor, initial decompression of the meningioma helps in dissection of the tumor off the optic nerve (**Fig. 11.6**). In many patients, the origin of tuberculum sellae meningiomas is eccentric and there is extension of tumor into the optic canal in the majority. The tumor extension in the optic canal must be removed to achieve a good visual outcome. Drilling of the roof of optic canal and sectioning the falciform ligament further allow removal of the tumor that extended into the optic canal. Some authors believe that initial optic canal deroofing may aid in optic nerve mobilization with minimal manipulation. When the tumor already encases the nerve or the nerve is already thinned out and stretched initial optic canal drilling appears to be appropriate before starting intratumoral decompression.[2]

It is important to realize that the tumor is covered by an arachnoid layer, which needs to be cut and mobilized before attempting tumor decompression. Tumor decompression can be performed through the carotico-optic corridor or inter-optic corridor. Tumor decompression can be done with either suction or Cavitron ultrasonic aspirator (CUSA), depending upon the tumor consistency. Occasionally, especially in large tumors, the tumor may be firm to hard and need cutting with fine sharp scissors. It is best to avoid using bipolar during decompression to avoid thermal injury to the optic nerve and perforators. Tumors extending posteriorly up to the diaphragm need to be dissected carefully safeguarding the pituitary stalk and the pituitary gland. If skull base mucosa is opened, it should be packed with fat/muscle and pericranium to prevent postoperative CSF leak.

Protection of Perforators

Initial identification of the ICA and gradual dissection of meningioma along the vessel up to the bifurcation is important. The ipsilateral A1 must be defined and gradual removal of the

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tumor should be done protecting the recurrent artery, Acom, and perforators (**Figs. 11.7** and **11.8**). Sharp dissection and cutting the tumor capsule should be done as slight traction at this point may result in inadvertent injury of the small perforators. In larger tumors, the vessels or perforators may appear encased and at risk of injury. In most of the cases, these vessels are outside the arachnoid layer. Identification of the arachnoid layer and dissection in the correct layer are necessary to avoid vascular injury.

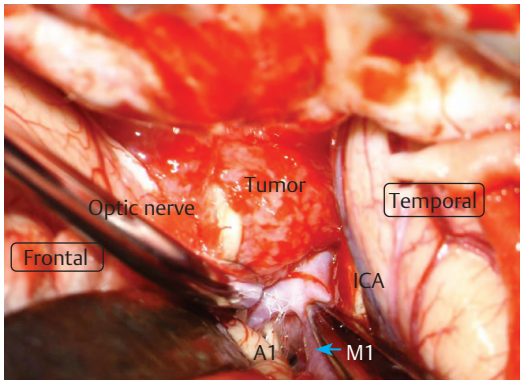

Fig. 11.7 Intraoperative image showing dissection of tumor along ipsilateral A1

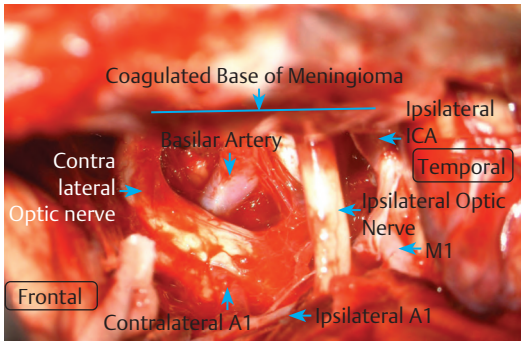

Fig. 11.8 Intraoperative image showing the coagulated skull base dura (attachment of meningioma). Note the contralateral optic nerve, both A1 and basilar artery visualized clearly after excision of the meningioma.

Complications

The tumor may be adherent to major vessels like ICA, A1, and M1. Injury to major vessels and perforators may result in postoperative focal neurological deficit. In larger tumors, the optic nerve may be thinned and already compromised. Any additional traction on optic nerve further deteriorates vision on that side. Intraoperative handling of the pituitary stalk may produce transient diabetes insipidus in the postoperative period. Although rare, opening of the sphenoid mucosa results in postoperative CSF rhinorrhea.

Comparison with Endoscopic Excision

Transcranial approach offers direct visualization of major vessels including perforators. In endonasal endoscopic excision, major perforators are encountered toward the end of the surgery. Dissection of artery/perforator encased by the tumor poses difficulty in dissection, and any bleeding may result in loss of endoscopic view. However, perforators can be visualized and thereby protected early in transcranial surgery and control of bleeding may be easier. Identification of the optic nerve and decompression of the tumor off the nerve can be done as an initial step of surgery. Moreover additional drilling of the optic canal and tumor decompression from the canal can be done at the beginning. The incidence of CSF leak in transcranial surgery is documented to be 2%, which is significantly less as compared to 9% in expanded endoscopic endonasal approaches. Transcranial approach has less chance of operative infection (4% vs. 9%) and olfactory dysfunction (7% vs. 22%) in comparison to that of endonasal approaches.[1,7]

In our opinion, larger tumors, tumors which are off the midline, and tumors which are likely to be firm or fibrous (as determined by MRI images) are better managed by transcranial approaches. Separation of the

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perforator vessels as well as preservation of pituitary stalk are better achieved with transcranial approaches.

References

1. Magill ST, McDermott MW. Tuberculum sellae meningiomas. Handb Clin Neurol 2020;170:13–23
2. Giammattei L, Starnoni D, Cossu G, et al. Surgical management of tuberculum sellae meningiomas: myths, facts, and controversies. Acta Neurochir (Wien) 2020;162(3):631–640
3. Chi JH, McDermott MW. Tuberculum sellae meningiomas. Neurosurg Focus 2003;14(6):e6
4. Lin PW, You W, Guo AS, Lin ZR, Wang YZ. Efficiency and safety of optic canal unroofing in tuberculum sellae meningiomas: a meta-analysis and systematic review. Neurosurg Rev 2023;46(1):240
5. Mahmoud M, Nader R, Al-Mefty O. Optic canal involvement in tuberculum sellae meningiomas: influence on approach, recurrence, and visual recovery. Neurosurg 2010;67:ons108–ons118; discussion ons118–109
6. Fahlbusch R, Schott W. Pterional surgery of meningiomas of the tuberculum sellae and planum sphenoidale: surgical results with special consideration of ophthalmological and endocrinological outcomes. J Neurosurg 2002; 96(2):235–243
7. Mastantuoni C, Cavallo LM, Esposito F, et al. Midline skull base meningiomas: transcranial and endonasal perspectives. Cancers (Basel) 2022; 14(12):2878

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12 Tuberculum Sellae Meningioma: Surgical Nuances of the Endoscopic Endonasal Approach and Recent Concepts

Chandrashekhar E. Deopujari, Archana Madhukar Kamble, Vikram Karmarkar, and Nishit Shah

Introduction

Tuberculum sellae meningioma accounts for 5 to 10% of all intracranial meningiomas. First reported by Steward in 1899 and in 1916, this tumor was first excised completely by Cushing.[1] The most common presentation is a visual disturbance[2] (80%), followed by headache (20–50%), endocrinological abnormalities (0–42%), less frequently seizures (2–3%), and behavioral changes (2–5%). The anatomical proximity of this tumor to the vital structures such as optic apparatus and pituitary stalk, and vascular encasement (internal carotid artery and anterior cerebral artery [ACA]) place special emphasis on surgical difficulties in complete resection of the tumor without postoperative neurological deterioration. This chapter reviews the minimally invasive endoscopic endonasal surgical aspects of tuberculum sellae meningioma and the recent concepts to consider while operating this tumor.

Anatomical Aspects

Tuberculum sellae is a part of the body of the sphenoid bone. It is a bony projection between the chiasmatic sulcus and sella turcica (**Fig. 12.1**). It is derived from the Latin word "tuber" which means "swelling" or "protuberance" above the sella. De Notaris et al[3] referred to it as the "suprasellar notch" when viewed inferiorly through the endoscopic transtubercular transplanum view. It is a groove-like depression between the superior margin of the sella and the posterior-most declining part of the planum sphenoidal. It is an indentation between the superior margin of sella turcica and the declining part of planum sphenoidal (**Fig. 12.2**). Suprasellar meningiomas are tumors arising from the suprasellar region and are named depending on the dura of the underlying structure. Tuberculum sellae meningioma comprises a meningioma arising from the tuberculum sellae, chiasmatic sulcus, and limbus sphenoidale. Many case series have described these tumors together with planum sphenoidal meningioma, dorsum sellae meningioma, and medial anterior clinoidal meningioma as common symptoms of the chiasmal syndrome.[2,4] However, surgical aspects of these tumors are different and anatomical considerations are important. The knowledge of intracranial bony landmarks of the suprasellar region and the corresponding extracranial parts in endoscopic panoramic view is important to assess the neurovascular anatomy intraoperatively. Tuberculum sellae meningioma causes compression of the optic apparatus and optic canal invasion laterally, displaces the pituitary stalk and chiasma posterosuperiorly, and encases the internal

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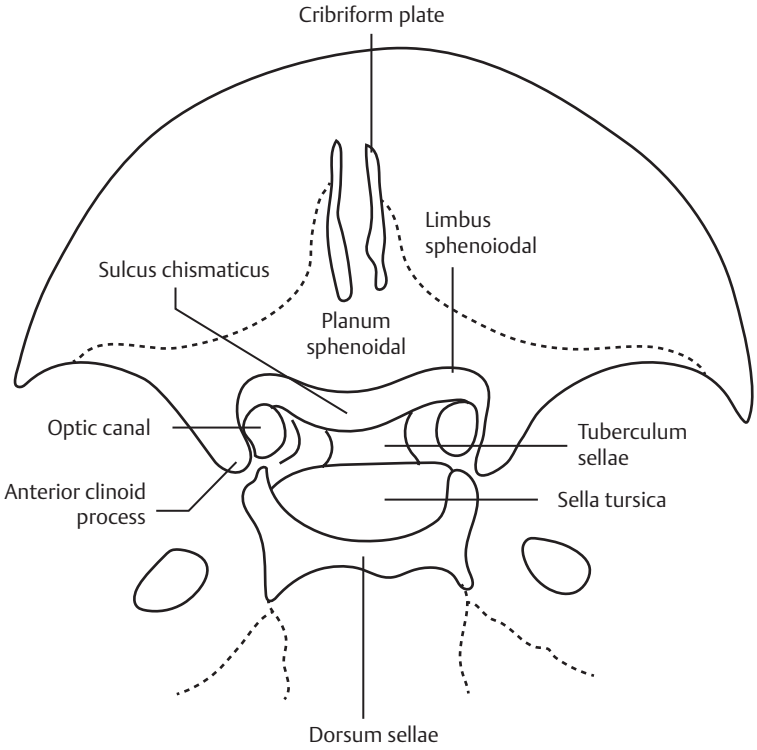

Fig. 12.1 Normal suprasellar anatomy.

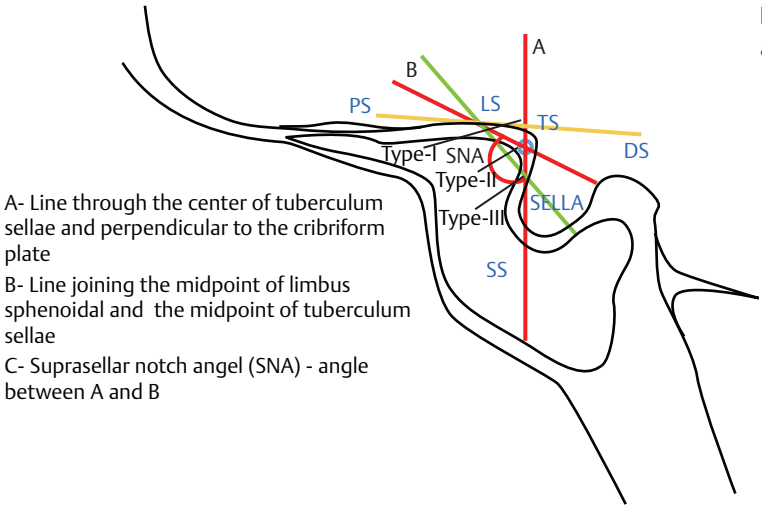

Fig. 12.2 Suprasellar notch and suprasellar notch angle.[3]

carotid artery and anterior cerebral arteries. As the tumor grows anteroposterior, it involves planum sphenoid anteriorly and sella and dorsum sellae posteroinferiorly. Laterally, it encases the internal carotid artery with cavernous sinus involvement and anterior cerebral arteries superiorly. The anatomical neurovascular relations of tuberculum sellae and the complexity of tumor play an important role in selecting an ideal surgical approach.

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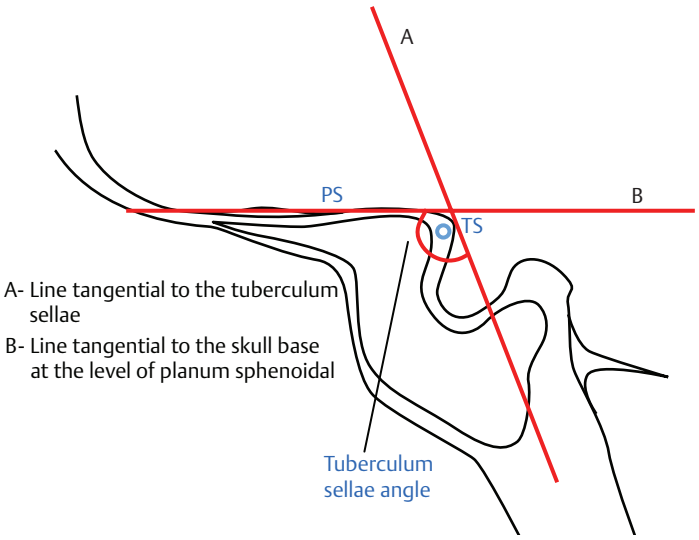

Fig. 12.3 Tuberculum sellae angle.[5,6]

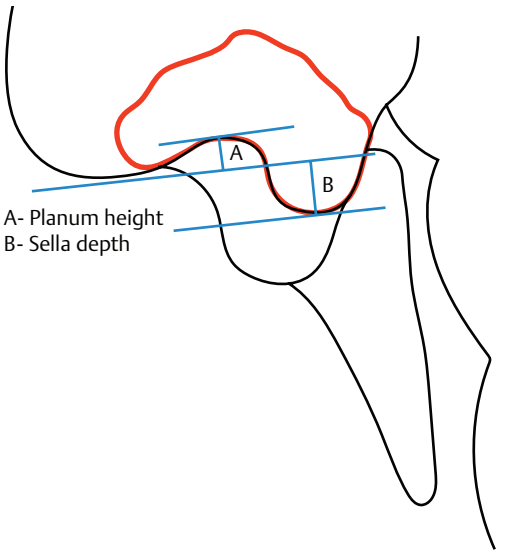

Fig. 12.4 Planum height and sella depth[7]—**(A)** planum height and **(B)** sella depth. Frontobasal line is the line joining anterior and posterior ends of the cribriform plate.

Radiological Assessment

The preoperative radiological information of tuberculum sellae meningioma on MRI and thin-cut CT scan of the brain gives a piece of vital information to decide the surgical plan. The size of the tumor, chiasmal compression, optic canal invasion, internal carotid artery encasement, dural tail length, brain invasion on FLAIR hyperintensities, hyperostosis of the underlying bone, and pneumatization of sphenoid sinus on preoperative MRI and CT scan guide the best approach for tuberculum sellae meningioma surgery. There are various case series which have described the surgical classification and grading systems for preoperative assessment of tumor. In 1938, Cushing[8] and Eisenhardt created the first surgical classification of tumors into four stages based on the tumor size, chiasmal deformity, and clinical presentation. Yasagil[2] recommended the classification of tumors based on tumor size with no consideration of neurovascular involvement. Mascarella et al[11] in a series of skull base meningioma proposed a simple predictability score system (**Table 12.1**) based on radiological measurements and findings for the prediction of the extent of resection of meningioma. They considered hyperostosis, the ratio of maximal dural length to interfovea ethmoidal distance, and the cavernous internal cerebral artery (ICA) involvement, and assigned a maximum score of 13. The authors categorized (**Table 12.1**) patients into low risk (score <6), intermediate risk (score 6–9),

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and high risk (score >9). Patients in the low-risk category showed a 100% probability of complete resection of meningioma. Goel et al in their series described clinicoradiological parameters for tumor grading.[12] The authors described the radiological parameters such as edema, vascular encasement (ICA and ACA), nature of the tumor, and hydrocephalus that could predict the possible difficulties in surgery. In their series Mortazavi et al[4] proposed a surgical classification score system for planum sphenoidal and tuberculum sellae meningioma surgery using preoperative MRI parameters (**Table 12.2**) such as tumor size, optic canal invasion, vascular encasement, FLAIR hyperintensities, previous radiation, and previous surgery. The total score ranges from 0 to 11. They classified tumors as

Table 12.1 Mascarella et al.[9] scoring system for predictability of resection of meningioma via endoscopic endonasal approach endonasal approach

Radiological factors	Radiological findings	Score
1. Bony status	Hyperostosis present	0
	Hyperostosis absent	1
2. Maximal dural tail length (MDTL) to inter-fovea ethmoidal distance ratio	<1.2	0
	1.2–2	2
	>2	6
3. Cavernous ICA involvement	No involvement	0
	Grade 2	3
	Grades 3 and 4	6

Abbreviation: ICA, internal cerebral artery.
Notes: Grade 2: Tumor extending beyond the intercarotid line, but not crossing the line beyond or tangential to the lateral aspects of the intra- and supracavernous ICA.
Grades 3 and 4: Tumor crossing beyond a tangential line formed by the lateral aspects of the intra- and supracavernous ICA.
Low risk (score <6)—100% probability of complete resection.
Intermediate risk (score 6–9)—60% probability of complete resection.
High risk (score >9)—0% probability of complete resection.
Adapted from: Mascarella et al.[11]

Table 12.2 Sekhar-Mortazavi tumor classification[4]

Parameters	0	1	2	4
Size	<2 cm	2–4 cm	>4 cm	-
Optic canal invasion	<5 mm	>5 mm	Complete	-
Vascular encasement	No	<180 degrees	>108 degrees	The maximum score for any combination >4
Brain invasion on MRI	No or mild FLAIR signal	Significant FLAIR signal	-	-
Previous surgery	No	Yes	-	-
Previous radiation	No	No	-	-

Total score: 0–11.
Scores: Class I: 0–3; Class II: 4–7; Class III: 8–11.
Vascular encasement (ICA and ACA).

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classes I, II, and III depending on the score. The high-class tumors (classes II and III) had high rates of intraoperative vascular injury and need for postoperative radiation. However, visual improvement was higher in cases of low-class tumors (class I). Some studies in the literature[2] have applied this classification and proved its efficacy in predicting surgical outcomes. Recently, Magill et al[13] proposed simple tumor grading scores (**Table 12.3**) and compared outcomes of different surgical approaches (both transcranial and endoscopic endonasal approaches). This scoring system is clinically feasible and simple to predict outcomes. Tumors with lower scores were resected by using a transsphenoidal approach and tumors with high scores were resected by using a more invasive and wider transcranial approach.

More recently, in their series of endoscopic endonasal approach to suprasellar meningioma, Youngerman et al[14] further studied the variables of surgical classifications of tuberculum sellae meningioma in detail and its relevance to the extent of resection of tumor. The authors studied Magill's grading system variables and used additional radiographic parameters (**Table 12.4**) to predict the extent of resection more accurately. They considered ICA and ACA encasement distinctly, proposed the "optic nerve laterality score," and considered anterior extension of tumor from limbus sphenoidal. They proposed the Weill Cornell SSM resectability score (**Table 12.4**). According to their study, prior surgery (independent nonradiographic significant risk factor), complete encasement of ICA, and extension of tumor lateral to the optic nerve are three significantly important radiographic

Table 12.3 Magill-McDermott (M-M) grading scale[13]

Tumor score	Score	Optic canal score	Score	Vascular encasement score	Score
<17 mm	1	No invasion or (≤3 mm)	0	Abuts medial wall only	0
>17 mm	2	Unilateral invasion (>3 mm)	1	Envelopes <180 degrees around the artery	1
		Bilateral invasion >3 mm	2	Envelopes ≥180 degrees around the artery	2

Table 12.4 Weill Cornell SSM resectability score[14]

Number	Radiographic features	Cut-off score	"P" value
1.	Max tumor diameter	>2 cm	0.265
2.	Anterior extension	>10 mm	0.352
3.	UCSF tumor diameter	>17 mm	0.617
4.	UCSF optic canal invasion	Unilateral or bilateral	0.068
5.	**Complete ICA encasement**	100% (score 3)	**0.017**
6.	ACA encasement	100% (score 3)	0.12
7.	**WC optic nerve laterality score**	100% (score 3)	**<0.0001**
8.	**Prior surgery (independent nonradiographic variable)**	Yes	**0.013**

Abbreviations: ACA, anterior cerebral artery; ICA, internal cerebral artery; SSM, suprasellar meningioma; UCSF, University of California, San Francisco grading; WC, Weill Cornell.

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risk factors that would predict gross total resection of tumor by endonasal endoscopic approach. The rest of the variables do not significantly reflect the probability of the extent of resection of tumor (**Table 12.4**).

De Notaris et al[3] have described (**Table 12.5**) the surgical importance of suprasellar notch (SSN) in endoscopic transsphenoidal surgery which is a complementary bony landmark of tuberculum sellae on the ventral (extracranial) aspect of the skull. They have described the suprasellar notch angle (SNA) (**Fig. 12.2**) as the angle between the line passing through the midpoint of tuberculum sellae, perpendicular to the cribriform plate, and the line passing through the midpoint of limbus sphenoidal and the midpoint of tuberculum sella. This angle measurement in preoperative CT scan and the lines measuring inter-optic distance at different levels help in surgical planning with approach and head positioning of the patient during surgery. As the SNA increases (**Fig. 12.2**), the inter-optic distance at the optic canal (IDOC) level decreases. Hence, an increased SNA favors the endoscopic endonasal approach but decreases the lateral wide exposure.

Some studies in the literature have studied the anatomical measurements in preoperative MRI and CT scans and planned surgeries accordingly to examine the extent of resection and visual outcomes postoperatively. Kong et al[7] described anatomical measurements (**Fig. 12.4**), planum height and sella depth, based on the tumor extension concerning the frontobasal line (**Fig. 12.4**) on preoperative MRI scan. Planum height (**Fig. 12.4**) of >5 mm are high-lying tumors, and the sella depth of >5 mm are low-lying tumors.

In their chapter, Deopujari et al have described[15] the criteria for case selection and contraindications for endoscopic endonasal approaches for suprasellar meningiomas (**Table 12.6**). In their case series of 12 patients

Table 12.5 De Notaris et al[3] classification

	Suprasellar notch angle (SNA)/ Tuberculum angle	Incidence	Approach	Head positioning	Lateral exposure	Reconstruction of skull base
Type I SNA	<118 degrees	16.6%	Transcranial	Extension (5–10 degrees)	Wide	Unfavorable
Type II SNA	118–138 degrees	70.8%	EETS	Neutral	Narrow	Favorable
Type III SNA	>138 degrees	12.5%	EETS	Flexion (5–10 degrees)	Limited	Optimal

Abbreviations: EETS, endoscopic endonasal transsphenoidal; SNA, suprasellar notch angle.

Table 12.6 Criteria for case selection for endoscopic endonasal approaches (EETS)

Indications for EETS	Relative contraindications for EETS
Small midline lesions (<2.5–3 cm)	Cavernous sinus involvement >270 degrees
Absence of parasellar extension	Bony hyperostosis
Optic canal involvement inferomedially	Active sinonasal infection
Sphenoid sinus extension	Conchal sphenoid sinus
	Preserved olfaction

Data from Deopujari et al.[15]

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with suprasellar meningioma managed by endoscopic approaches, there were 91.6% gross total resection and visual improvement was seen in all patients with no CSF leak.

In their review of the endoscopic endonasal approach to anterior cranial fossa meningioma, Michael B. Avery and colleagues[16] proposed criteria for patient selection and surgical considerations for endoscopic endonasal approach and transcranial supraorbital approach based on preoperative imaging. Patients with majority of the tumor below the planum, tuberculum angle <135 degrees (**Fig. 12.3**), midline tumors with minimal to no lateral extension beyond the medial margin of supraclinoid ICA, and hyperostotic tuberculum sellae, with or without optic canal invasion, are considered to have favorable anatomical aspects for the endonasal endoscopic approach.

In their series, Gardner et al[17] also stated that the preoperative MRI findings significantly determine the outcomes of the endoscopic transsphenoidal approach to anterior cranial fossa meningiomas. The tumor size, subpial invasion of brain parenchyma with FLAIR hyperintensities, absence of cortical cuff, and direct overlying of A2 and frontopolar artery branches over the tumor capsule, involvement of underlying bone with hyperostosis, and long dural tail in transverse section greatly influence the extent of tumor resection.

At our institute, we perform routine imaging protocol for suprasellar meningioma with preoperative contrast MRI scans (**Fig. 12.5**) and CT scans with CT angiogram (**Fig. 12.6**). We assess preoperative MRI scans to look for the tumor location, contrast enhancement, and dural tail length. On axial sections and coronal sections, look for the optic canal invasion and vascular encasement. On T2/FLAIR images, look for vascular relations of tumor, cortical cuff, consistency of tumor, subpial invasion of tumor, and peritumoral parenchymal edema. CT scan is performed to look for tumor calcifications, underlying bone hyperostosis (**Fig. 12.6**), pneumatization of sinuses, and for surgical planning in cases of redo surgeries. CT angiogram (**Fig. 12.6**) provides information about the vascular supply of the tumor and the relation of the tumor with major vessels. We have chosen a transcranial approach due to MRI features (**Fig.12.7a**) suggestive of a long dural tail in transverse diameter in the coronal section, bilateral carotid artery encasement with cavernous sinus extension, and the absence of cortical cuff between the tumor and ACA branches on the superior aspect of the tumor. We have selected the patient for the endonasal approach due to MRI features (**Fig.12.7b**) on coronal sections suggested a small midline suprasellar tumor with no carotid encasement or optic canal invasion and low-lying tumor with less anterior extension on sagittal sections.

In his chapter on meningioma in the book *WFNS Guide for Neuroendoscopy*, Roman Bosnjak[8] also described the technique of opening optic nerve sheath (dural sleeves) at the superior aspect with angled microscissors or cutting knife to avoid injury to the ophthalmic artery and radically removing tumor from the inferomedial aspect of the optic canal. He also stated that the variables tumor size, optic canal invasion, and carotid artery and ACA encasement are important keys for this surgery, which influence the difficulty in resection of the tumor, while the brain invasion with no cortical cuff and FLAIR hyperintensities on MRI scan, peritumoral edema, previous surgery or radiation, and duration of visual impairment are prognostic factors that influence the extent of tumor resection.

Surgical Approaches

Tuberculum meningioma is resected by transcranial and transsphenoidal approaches. The transcranial approaches used are bifrontal, subfrontal, frontolateral, pterional, and minimal invasive supraorbital keyhole approaches. The pterional and frontolateral approaches are the most commonly applied transcranial routes. The literature has many studies[18,19] that offer different surgical approach considerations for

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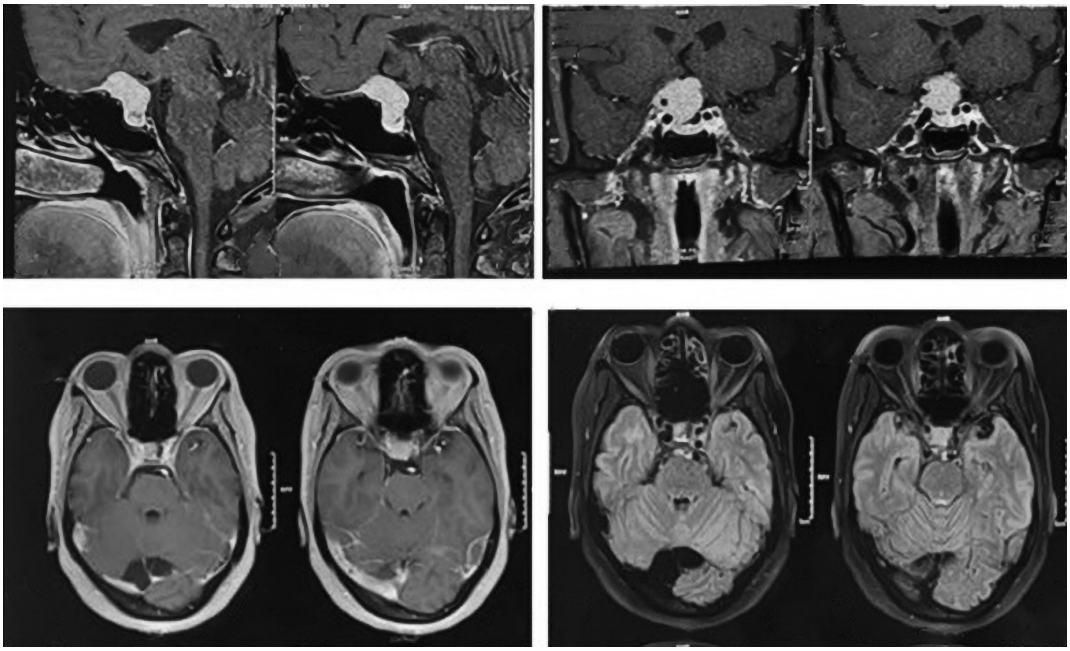

Fig. 12.5 MRI scan (our imaging protocol) showing suprasellar tumor homogenously enhancing with dural tail and extension to right cavernous, encasing carotid artery.

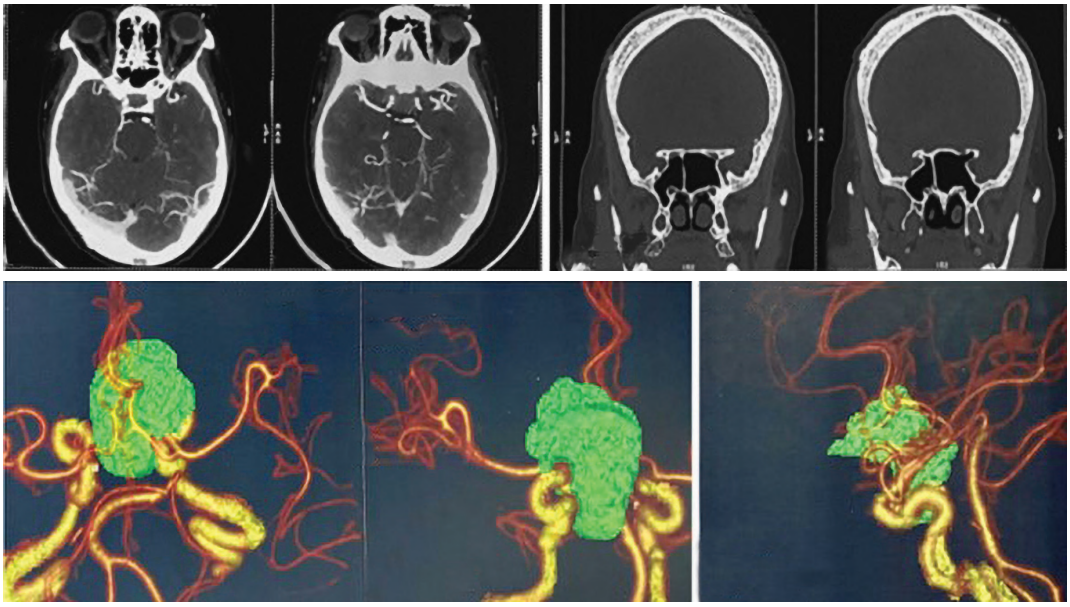

Fig. 12.6 CT scan and CT angiogram (our imaging protocol) showing hyperostosis of the frontal bone and tumor encasing carotid artery and anterior cerebral artery branches.

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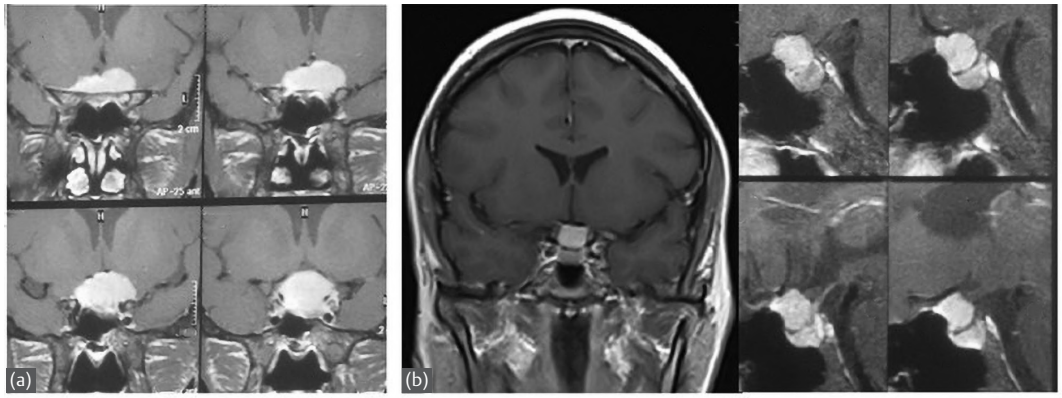

A- Pterional approach

B- Endoscopic endonasal approach

Fig. 12.7 Choice of approach (transcranial vs. endoscopic endonasal approach). **(a)** A large tumor, with long dural tail length in transverse diameter and absence of cortical cuff with ACA branches, was chosen for the transcranial pterional approach. **(b)** A small midline tumor with no vascular encasement in the coronal section and more sellar extension in the sagittal section is favorable for endoscopic endonasal approach.

tuberculum sellae meningioma surgery. In modern microneurosurgical advanced practice, the disadvantage of more brain retraction by transcranial approaches has decreased. The small tumor with less complexity is resected endoscopically from below through the endoscope-assisted transnasal transsphenoidal microscopic approach, endonasal endoscopic transsphenoidal approach, and translabial transseptal transsphenoidal approach.

Endoscopic Endonasal Transsphenoidal Approach

The extended endonasal transsphenoidal approaches and the renewed skull base reconstruction techniques have made the greater resection of tumor with CSF leak and vascular complications less possible. The tuberculum sellae meningiomas with extension posteroinferiorly into sella and dorsum sellae, the vertical diameter of tumor less than 3 cm, not extending laterally to the internal carotid artery and optic canal, and with narrow dural tail length are better approached from below by endoscopic endonasal transsphenoidal route. This approach gives a wide panoramic view with a direct approach to the inferomedial part of the optic canal, which is the most commonly invaded portion of the optic canal by tuberculum sellae meningioma. This approach also allows early devascularization of the tumor, prevents damage to ICA and ACA arterial branches, and causes less brain retraction. However, there is a high risk of CSF leak and meningitis due to this potentially contaminated route. The recent advances in the reconstruction of the skull base have reduced the risk of CSF leak to a minimal extent. Although many surgical advances and developments are evolving in the neuroendoscopic field, patient selection is a very crucial part of the surgery. We have shared our experience below with a discussion of a few select cases of tuberculum sellae meningioma operated by the endonasal endoscopic approach. The detailed operative technique is well described by our team previously in "Operative Neuroendoscopy Atlas."[15]

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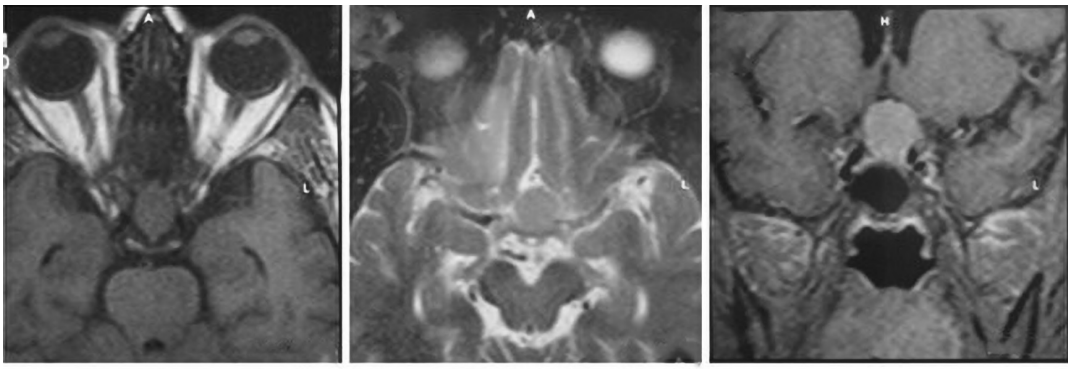
Case 1: Tuberculum Sellae Meningioma Confined to Tuberculum Sellae Region

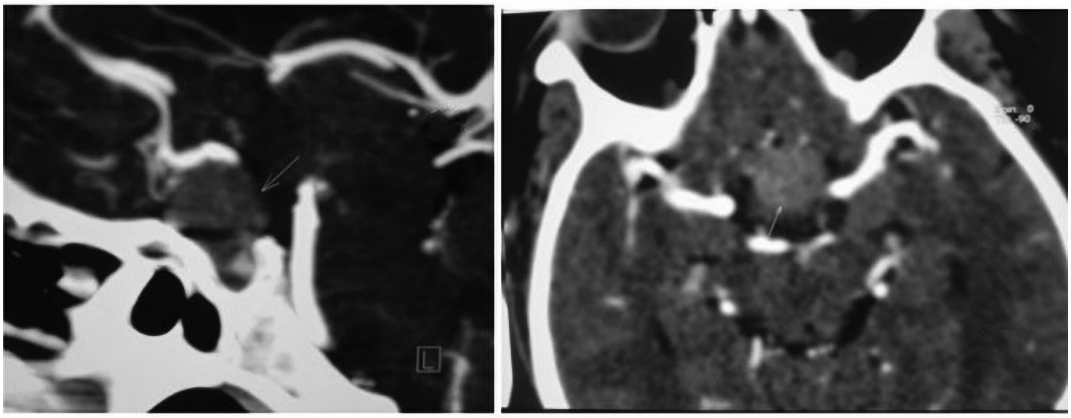
A 68-year-old female patient presented with blurring of vision and headache. She had left temporal visual field defects. Preoperative MRI of brain was suggestive of suprasellar dural-based homogenously enhancing tuberculum sellae meningioma, indenting bilaterally on the medial wall of the optic canal, more on the left side, with no optic canal invasion or vascular encasement (**Fig. 12.8**).

Intraoperatively, the tumor was approached through a transplanum transtuberculer approach, and planum sphenoidal and tuberculum sellae were drilled out (**Fig. 12.9**). Superior intercavernous sinus coagulated and cut. Dura opened and tumor decompression started. Complete excision of the tumor was confirmed. Optic apparatus was decompressed and the floor of the third ventricle was visualized with preservation of normal pituitary gland. Skull base reconstruction was done by using fascia lata, glue, and gelfoam (**Fig. 12.10**).

The patient's vision was completely recovered postoperatively and showed no residual tumor on postoperative CT and MRI brain scan (**Fig. 12.11a, b**).



MRI- Brain



CT- Angiography brain

Fig. 12.8 MRI and CT angiography of brain of a 68-year-old woman with tuberculum sellae meningioma.

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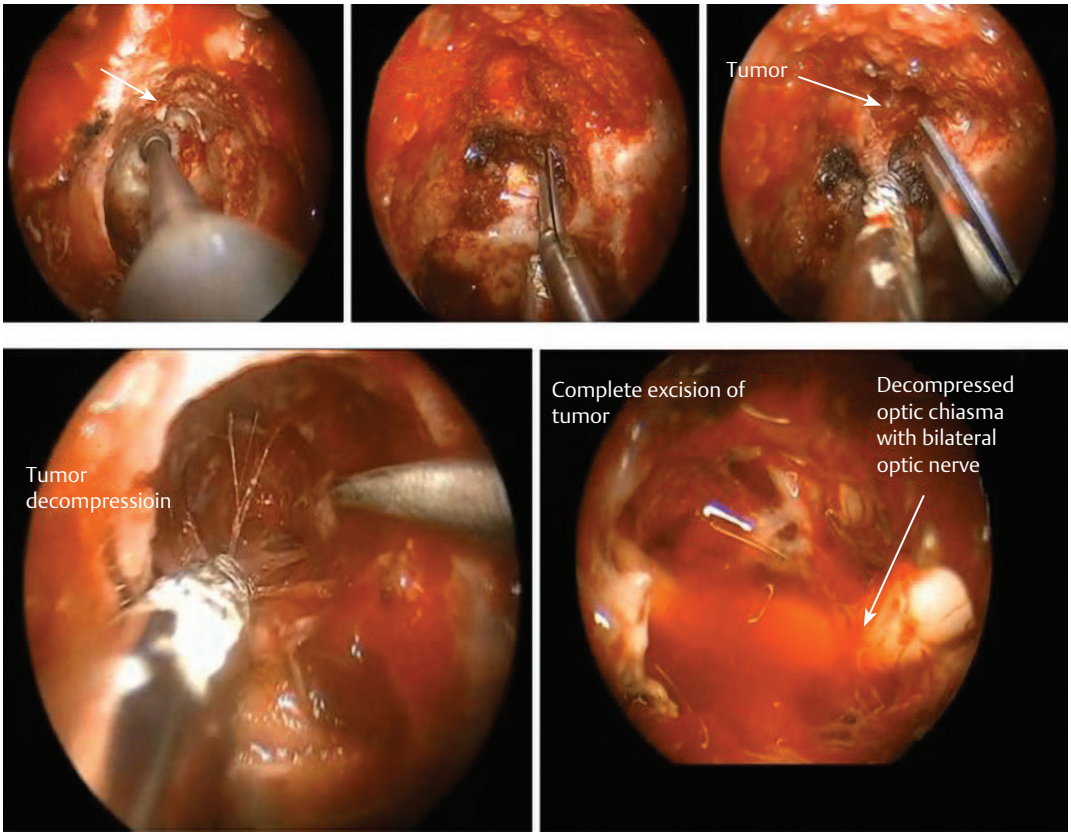

Fig. 12.9 Intraoperative images (labelled) of a 68-year-old woman with tuberculum sellae meningioma showing complete excision of the tumor and decompressed optic apparatus.

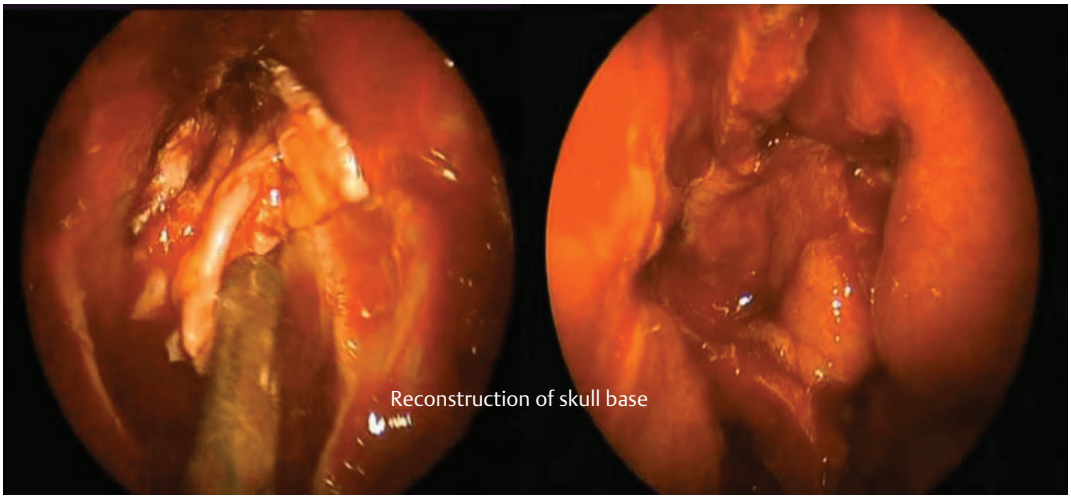

Fig. 12.10 Skull base reconstruction of a 68-year-old woman with tuberculum sellae meningioma.

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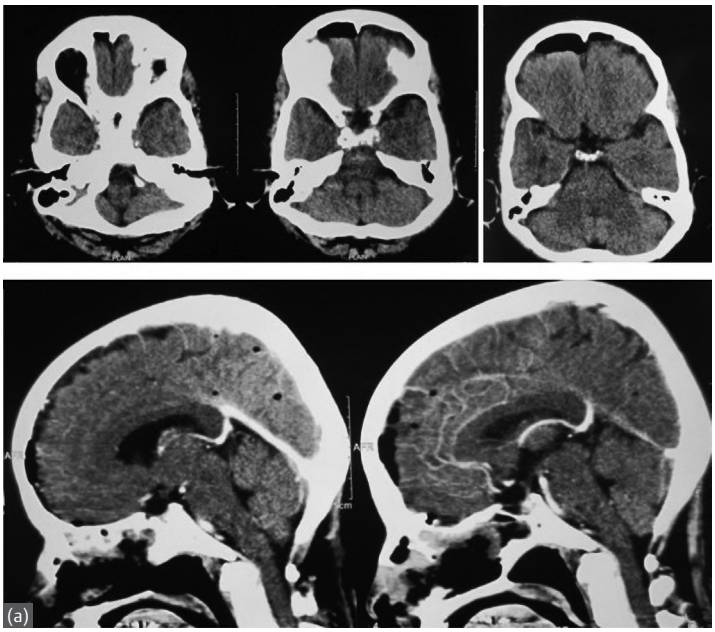

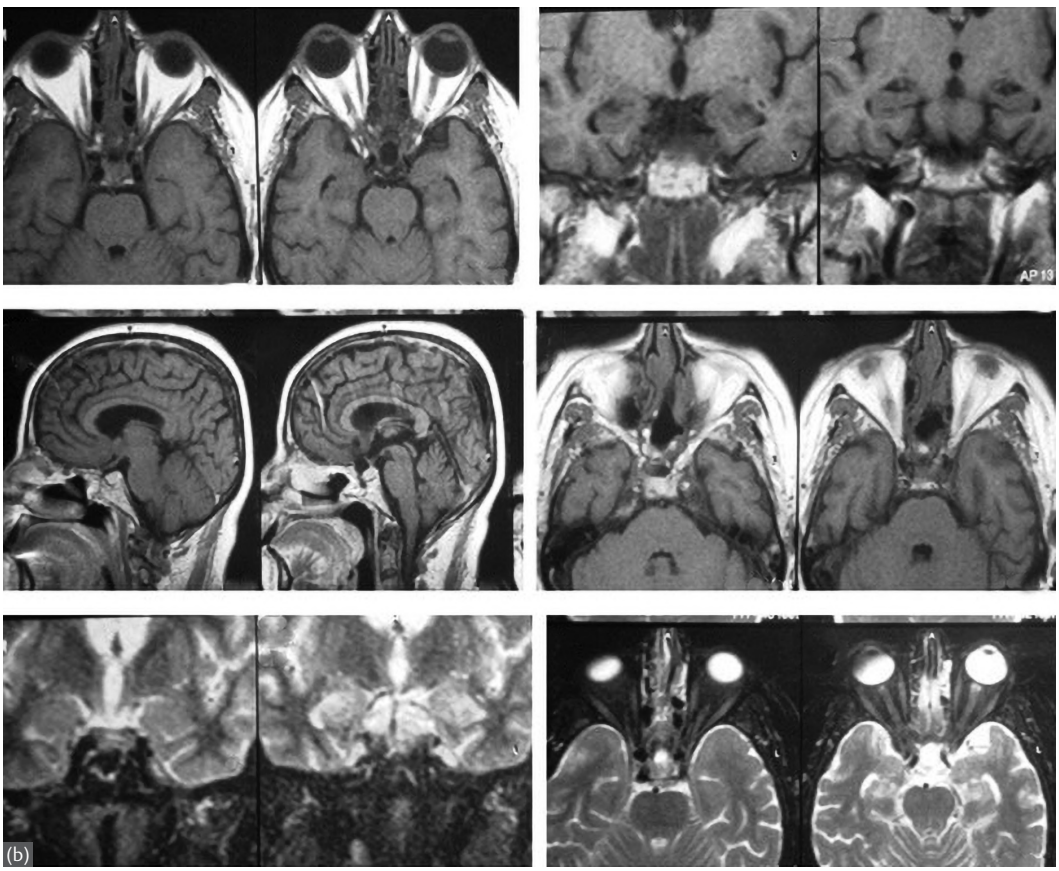

Fig. 12.11 (a) Postoperative CT scan of brain of a 68-year-old woman with tuberculum sellae meningioma showing no hematoma, no residual tumor. **(b)** Postoperative MRI of brain of a 68-year-old woman with tuberculum sellae meningioma showing no residual tumor.

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Case 2: Tuberculum Sellae Meningioma Extending Medial to Internal Carotid Artery Going into the Optic Canal

A 47-year-old female patient presented with giddiness and mild headache. MRI of brain showed a right-sided tuberculum sellae dural-based homogenously enhancing lesion, medial to the internal carotid artery and extending into the medial portion of the optic canal (**Fig. 12.12**).

The tumor was approached through an endoscopic endonasal approach. After posterior ethmoidectomy, the right side medial opticocarotid recess was confirmed, and the drilling of planum sphenoidal and tuberculum sellae bone was performed (**Fig. 12.13a**). Dura was opened and the intercavernous sinus coagulated and cut. The tumor was identified and dissected in its left margin and separated far from the pituitary gland (**Fig. 12.13b**).

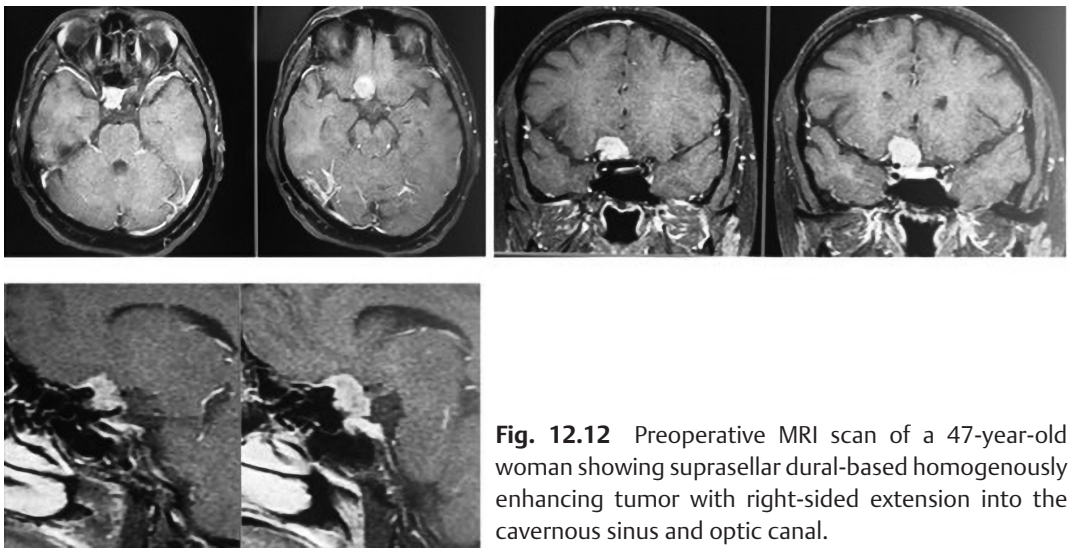

Fig. 12.12 Preoperative MRI scan of a 47-year-old woman showing suprasellar dural-based homogenously enhancing tumor with right-sided extension into the cavernous sinus and optic canal.

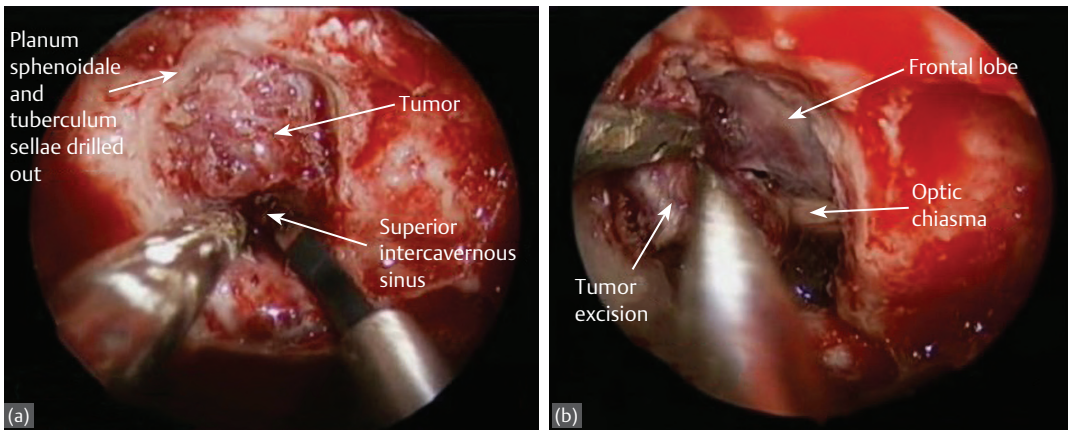

Fig. 12.13 **(a, b)** Intraoperative (labelled) images of a 47-year-old woman with tuberculum sellae meningioma showing steps of optic canal decompression and removal of the tumor. (*Continued*)

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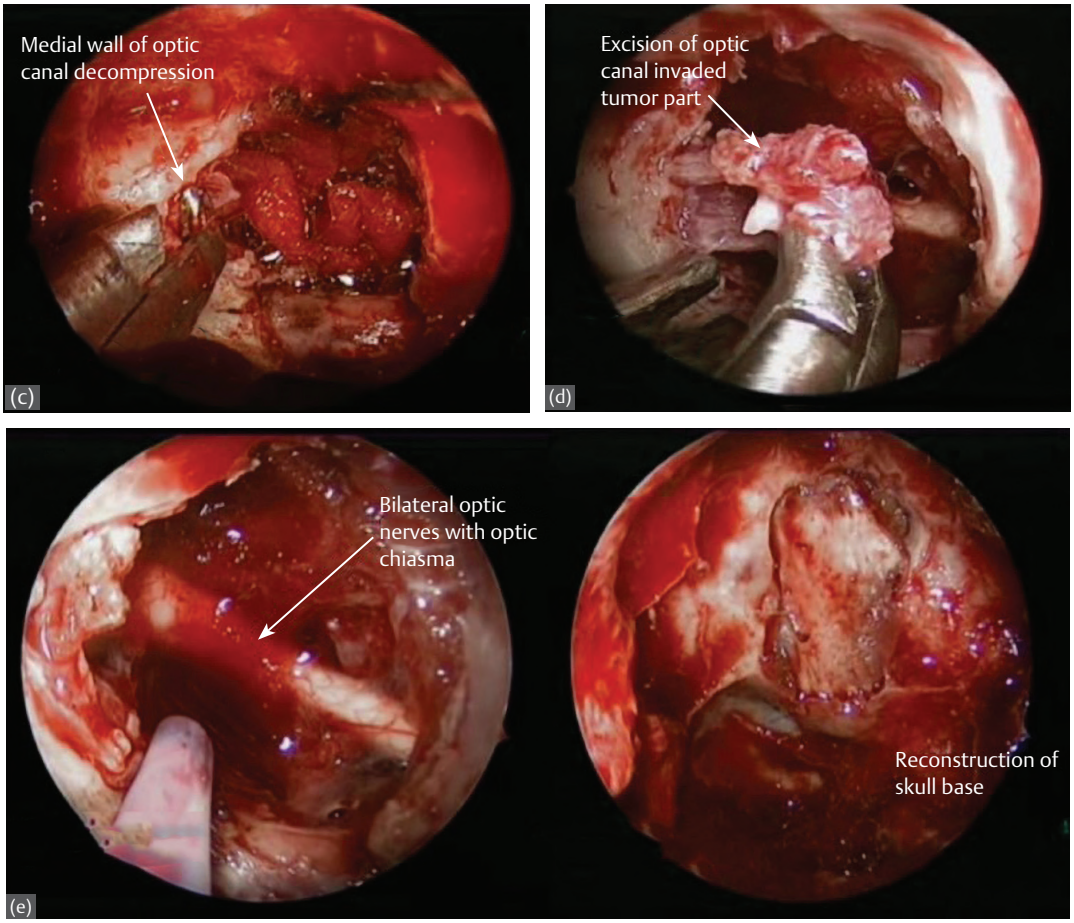

Fig. 12.13 (*Continued*) **(c, d)** Intraoperative (labelled) images of a 47-year-old woman with tuberculum sellae meningioma showing steps of optic canal decompression and removal of the tumor. **(e)** Intraoperative (labelled) images of 47-year-old-woman showing complete excision of the tumor and reconstruction of the skull base.

The tumor was excised. The medial wall of the optic canal was punched out (**Fig. 12.13c**) and the canal decompressed to excise the part of the tumor going into the optic canal. Gross total excision of the tumor was done (**Fig. 12.13d, e**). Reconstruction of skull base was done (**Fig. 12.13e**).

Postoperatively, the patient had no deterioration of vision and no CSF leak and was discharged home.

Case 3: Recurrent Tuberculum Sellae Meningioma

A 52-year-old woman presented with a diminution of bilateral vision, more in the left eye than the right eye with bitemporal hemianopia. The MRI of brain (**Fig. 12.14**) was suggestive of a suprasellar lesion based on planum sphenoidal and tuberculum sellae, with homogenous enhancement. She underwent gross tumor

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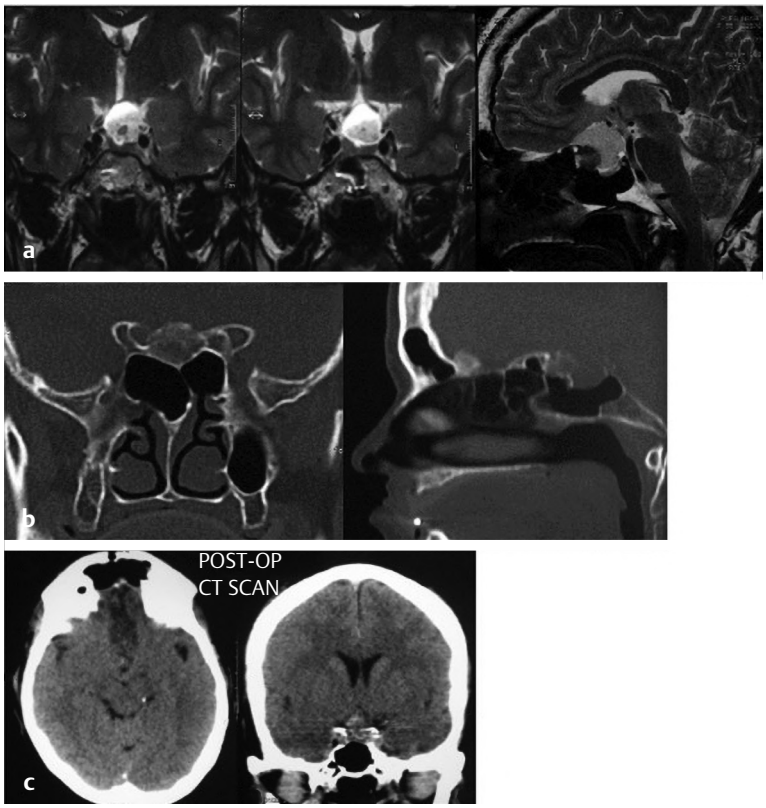

Fig. 12.14 **(a)** Preoperative MRI of brain of a 52-year-old woman with tuberculum sellae meningioma showing heterogeneously enhancing well-defined tumor with anterior extension to planum sphenoidal. **(b)** CT scan showing hyperdense suprasellar lesion with minimal hyperostosis. **(c)** Postoperative CT scan showing bifrontal edema.

resection of meningioma through a bifrontal interhemispheric approach (**Fig. 12.14**). Postoperatively, the patient deteriorated with drowsiness and seizures, and the CT scan was suggestive of bilateral frontal lobe edema. Bifrontal decompressive craniectomy was done. The patient's Glasgow Coma Scale (GCS) was improved postoperatively and discharged. There was visual improvement in bilateral eyes on follow-up visits.

After 7 years postoperatively, she presented with deterioration of vision and recurrent tuberculum sellae meningioma on MRI scan (**Fig. 12.15**). Since the tumor was confined to the midline suprasellar region and medial to the medial wall of the internal carotid artery and optic canal, she underwent endoscopic endonasal approach and tumor excision. The tumor was approached through transsphenoidal transtubercular approach (**Fig. 12.16**).

There was an improvement in vision postoperatively. However, residual tumor was there on the postoperative follow-up MRI scan. The patient was planned for gamma knife surgery for the residual tumor after confirmation of delineation of the optic nerve and no residual part was left in the optic canal.

Transcranial Approaches versus Endoscopic Approaches

The literature has contributed many case series comparing the outcomes of approaching tumor from above and below. The recent metanalysis and case series showed better visual outcomes by the endoscopic approach (EEA) than the transcranial approach (TCA),

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carrying the risk of CSF leak and meningitis endoscopically. Gardner et al[17] in a series of endoscopic management of anterior cranial fossa meningiomas showed that endoscopic approach is more feasible for Simpson's grade I resection due to more resection of involved hyperostotic bone and dura, early devascularization of the tumor, and less handling of compressed neurovascular structures and brain parenchyma giving better postoperative

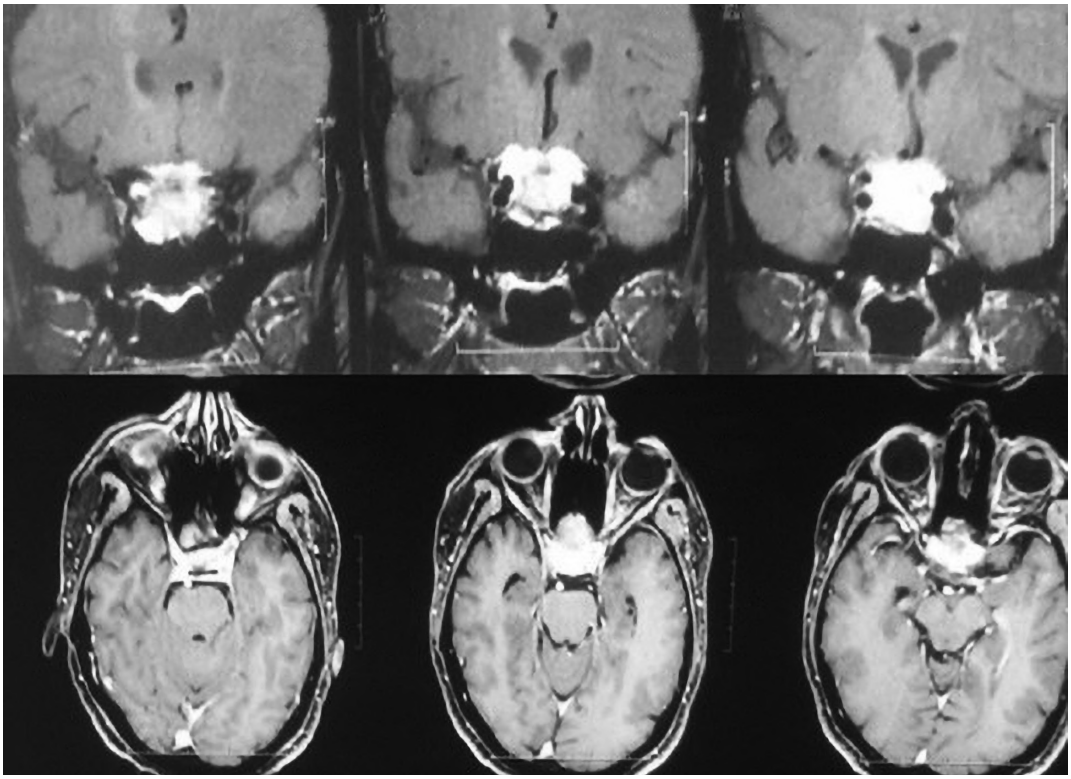

Fig. 12.15 Postoperative MRI of brain (coronal and axial images) of a 52-year-old woman with tuberculum sellae meningioma showing recurrent meningioma.

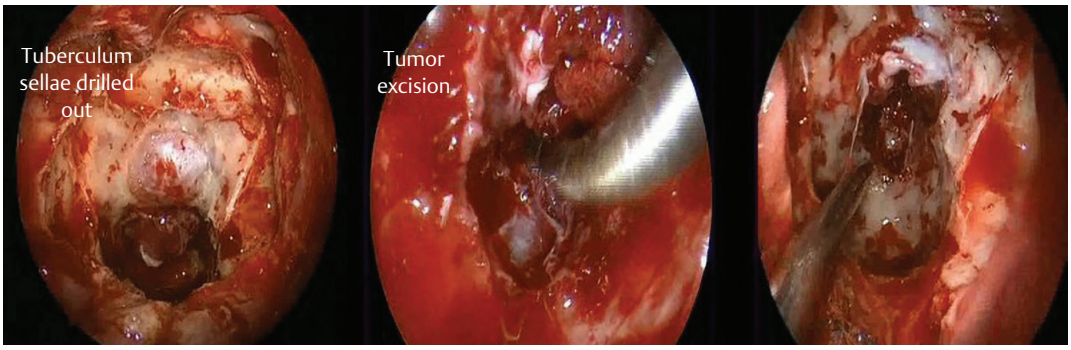

Fig. 12.16 Intraoperative images (labelled) of a 52-year-old woman with recurrent tuberculum sellae meningioma showing steps of gross total tumor excision.

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visual outcomes. Divitiis et al[20] described the criteria for the endoscopic endonasal approach for tuberculum sellae meningioma as small to medium size tumors with limited dural attachment and no vascular encasement. Series by Bowers et al[21] and Komotar et al[22] also supported the criteria for EEA and stated that the endoscopic approach should not be the approach to tumors more than 3 cm in diameter, extending lateral to the internal carotid artery, underlying the ACA, and having dural attachments superolateral to the optic canal. Kong et al[7] proposed anatomical measurements of tumors on preoperative MRI scans (**Fig. 12.4**) and concluded that high-lying tubercular meningioma was better approached by the transcranial route while low-lying tumors were best approached by EEA. Magill et al[11] in their series studied the cases of two large centers, compared both the approaches, and proposed a simple clinically feasible tumor grading score system (**Table 12.3**) to plan the surgical strategy in tuberculum sellae meningioma.

The authors found no significant difference in the visual outcome through either of the approaches. However, they proposed that the visual outcomes mostly depend on the complexity of the tumor, the surgeon's preference, and the goal of surgery. There are various studies[14,23] and discussions[21] about the reliability of the parameters of this simple tumor grading scoring system in the literature. Youngerman et al[14] proposed a new scoring system (**Table 12.4**) and stated that the pure endoscopic endonasal approach case series studies are necessary for the exact prediction of the extent of resection through the endonasal route. According to this system, the tumor size, optic canal invasion, incomplete ICA invasion, ACA branches invasion, brain edema, and presence of cortical cuff do not determine the extent of resection reliably. However, the history of previous surgery, complete ICA encasement (360 degrees), and tumor lateral to the optic nerve have a significant relation with a gross total extension of the tumor (**Table 12.4**). The authors achieved radiographic complete resection of the tumor in 85% of patients and microscopic resection in 79% of patients in the absence of these significant risk factors. However, the endoscopic endonasal extent of resection through radiographic imaging score was not found similar to Simpson's grading system.[14] In their series, Kshettry et al[24] also showed that tumors extending superior and lateral to the optic canal are better addressed by the transcranial route whereas tumors lateral to the optic canal are a contraindication to the endoscopic endonasal approach. Tumors with prefixed optic chiasma are considered a good indication for an endoscopic endonasal approach. Gupta et al[25] also concluded that the select group of patients having tumor size less than 2.5 to 3 cm, lateral vascular encasement less than 270 degrees with absent parasellar extension, only inferomedial optic canal invasion, and sphenoid sinus extension benefit from endoscopic endonasal approaches. A systematic review analysis of tuberculum sellae meningioma surgery was performed by Mazada K. Turel[26] and colleagues and found that transcranial approaches are considered gold standard approaches although endoscopic approaches and endoscope-assisted approaches are favorable in the greater resection of tumor with better visual outcomes. However, the diversities in case series make it difficult to directly compare transcranial and endoscopic approaches in similar cohorts of patients. Despite various studies reported in the literature comparing transcranial and endoscopic transnasal approaches for tuberculum sellae meningioma, a true comparison for the postoperative visual outcomes and extent of resection of tumor is not possible due to the small-scale sample size, patient selection bias, and lack of uniformity in surgical classifications and tumor grading systems used all over the world.

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Endoscope-Assisted Transcranial Minimal Invasive Approaches

Apart from the purely endoscopic endonasal approach for tuberculum sellae meningioma, the endoscope-assisted transcranial minimally invasive approach has its value. The literature has described better postoperative visual outcomes and greater extent of resection of tumor in cases of endoscope-assisted minimally invasive transcranial surgery for large complex tumors than purely microsurgical transcranial surgeries. In their series Marx et al[27] described endoscope-assisted frontolateral and supraorbital transcranial approaches and confirmed better visual outcomes with less endocrinological dysfunctions due to endoscope-assisted surgeries providing an excellent panoramic view of hidden areas, less manipulation of optic apparatus, and preservation of perforator arteries of chiasma and hypophysis. The authors reported 90.9% improvement in visual acuity, 90% improvement in visual deficits, and no deterioration. Kumar et al[28] have also supported the concept of endoscopic assistance in transcranial approaches (from our institutional experience) for suprasellar meningioma. They reported 91.7% Simpson's grade I and II resection and 8.3% grade III resection. About 66% of patients had improved vision while 40% remained the same.

Summary

The surgical approaches for resection of tuberculum meningioma are progressively improving the extent of resection of tumor with minimal vascular and optic nerve damage and better visual outcomes. The endoscope has always been an additional benefit in both endoscopic endonasal as well as transcranial approach micro-neurosurgery. The recent advances, preoperative high-quality radioimaging and assessment, advanced modern angled endoscopes, excellent panoramic three-dimensional view, and renewed distinct endoscopic instruments made it possible for Simpson's grade I resection of tuberculum sellae meningioma. However, proper selection of patients, individualization of the case, preoperative clinicoradiological assessment, and surgeons' skill and experience are the key to the ideal approach for tuberculum sellae meningioma surgery.

References

1. Kachhara R, Nigam P, Nair S. Tuberculum sella meningioma: surgical management and results with emphasis on visual outcome. J Neurosci Rural Pract 2022;13(3):431–440
2. Giammattei L, Starnoni D, Cossu G, et al. Surgical management of tuberculum sellae meningiomas: myths, facts, and controversies. Acta Neurochir (Wien) 2020;162(3):631–640
3. de Notaris M, Solari D, Cavallo LM, et al. The "suprasellar notch," or the tuberculum sellae as seen from below: definition, features, and clinical implications from an endoscopic endonasal perspective. J Neurosurg 2012;116(3):622–629
4. Mortazavi MM, Brito da Silva H, Ferreira M Jr, Barber JK, Pridgeon JS, Sekhar LN. Planum sphenoidale and tuberculum sellae meningiomas: operative nuances of a modern surgical technique with outcome and proposal of a new classification system. World Neurosurg 2016;86:270–286
5. Zada G, Agarwalla PK, Mukundan S Jr, Dunn I, Golby AJ, Laws ER Jr. The neurosurgical anatomy of the sphenoid sinus and sellar floor in endoscopic transsphenoidal surgery. J Neurosurg 2011;114(5): 1319–1330
6. Brahimaj BC, Wong AK, Joshi KC, Byrne RW, Beer-Furlan A. Tuberculum sellae angle: assessing caudal reach of the supraorbital keyhole craniotomy in tuberculum sella meningiomas. J Neurol Surg B Skull Base 2022;83(S 01):S1–S270
7. Kong DS, Hong CK, Hong SD, et al. Selection of endoscopic or transcranial surgery for tuberculum sellae meningiomas according to specific anatomical features: a retrospective multicenter analysis (KOSEN-002). J Neurosurg 2019;130(3): 838–847
8. Bosnjak R. Endoscopic endonasal excision of meningiomas. In: Deopujari C, Qureshi M, Thombre B, eds. WFNS Guide for Neuroendoscopy.

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Mumbai, Maharashtra: Salubris Medical Publishers; 2022:116–119
9. Cushing EL H. Suprasellar meningiomas. In: Thomas CC (ed) Meningiomas: Their Classification, Regional Behavior, Life Hystory, and Surgical End Results. Elsevier Inc., Baltimore 1938; p 25
10. MG Y. In: Microneurosurgery in four volumes, vol 4B. Thieme Medical Publisher, New York; 1996
11. Mascarella MA, Tewfik MA, Aldosari M, Sirhan D, Zeitouni A, Di Maio S. A simple scoring system to predict the resectability of skull base meningiomas via an endoscopic endonasal approach. World Neurosurg 2016;91:582–591.e1
12. Goel A, Muzumdar D, Desai KI. Tuberculum sellae meningioma: a report on management on the basis of a surgical experience with 70 patients. Neurosurgery 2002;51(6):1358–1363, discussion 1363–1364
13. Magill ST, Morshed RA, Lucas CHG, et al. Tuberculum sellae meningiomas: grading scale to assess surgical outcomes using the transcranial versus transsphenoidal approach. Neurosurg Focus 2018;44(4):E9
14. Youngerman BE, Banu MA, Gerges MM, et al. Endoscopic endonasal approach for suprasellar meningiomas: introduction of a new scoring system to predict extent of resection and assist in case selection with long-term outcome data. J Neurosurg 2020;135(1):113–125
15. Deopujari CE, Shaikh ST, Karmarkar VS, Shah NJ. Endonasal endoscopic surgery for suprasellar meningiomas. In: Yadav YR, Sharma BS, Bajaj J, eds. Neuroendoscopic Surgery—A Comprehensive Approach. Vol 2. Noida, Uttar Pradesh: Salubris; 2020:288–292
16. Avery MB, Barkhoudarian G, Kelly DF. Endoscopic endonasal surgery for anterior skull base meningiomas. Mini Invasive Surg 2021;5:17
17. Gardner PA, Kassam AB, Thomas A, et al. Endoscopic endonasal resection of anterior cranial base meningiomas. Neurosurgery 2008;63(1): 36–52, discussion 52–54
18. Nakamura M, Roser F, Struck M, Vorkapic P, Samii M. Tuberculum sellae meningiomas: clinical outcome considering different surgical approaches. Neurosurgery 2006;59(5):1019–1028, discussion 1028–1029
19. Chokyu I, Goto T, Ishibashi K, Nagata T, Ohata K. Bilateral subfrontal approach for tuberculum sellae meningiomas in long-term postoperative visual outcome. J Neurosurg 2011;115(4):802–810
20. de Divitiis E, Esposito F, Cappabianca P, Cavallo LM, de Divitiis O, Esposito I. Endoscopic transnasal resection of anterior cranial fossa meningiomas. Neurosurg Focus 2008;25(6):E8
21. Bowers CA, Altay T, Couldwell WT. Surgical decision-making strategies in tuberculum sellae meningioma resection. Neurosurg Focus 2011; 30(5):E1
22. Komotar RJ, Starke RM, Raper DMS, Anand VK, Schwartz TH. Endoscopic endonasal versus open transcranial resection of anterior midline skull base meningiomas. World Neurosurg 2012; 77(5-6):713–724
23. Almeida JP, Gentili F. Letter to the Editor. Grading scale for tuberculum sellae meningiomas. Neurosurg Focus 2018;45(3):E13
24. Kshettry VR, Elshazly K, Evans JJ. Endoscopic transnasal surgery for planum and tuberculum sella meningiomas: decision-making, technique and outcomes. CNS Oncol 2016;5(4):211–222
25. Gupta PP, Shaikh ST, Deopujari CE, Shah NJ. Transnasal endoscopic surgery for suprasellar meningiomas. Neurol India 2021;69(3):630–635
26. Turel MK, Tsermoulas G, Yassin-Kassab A, at al. Tuberculum sellae meningiomas: a systematic review of transcranial approaches in the endoscopic era. J Neurosurg Sci 2019;63(2):200–215
27. Marx S, Clemens S, Schroeder HWS. The value of endoscope assistance during transcranial surgery for tuberculum sellae meningiomas. J Neurosurg 2018;128(1):32–39
28. Kumar A, Deopujari CE, Karmarkar VS. A review of anterior interhemispheric subfrontal approach in management of suprasellar meningiomas with endoscopic assistance. Internet J Neurosurg 2009;7(2)

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13 Asymptomatic Carotid Stenosis

Paritosh Pandey, Saurabh Sinha, Parth Joshi, Ullas V. Acharya, and Pallavi Nyalkalkar

Introduction

Asymptomatic carotid artery stenosis (aCAS) is defined as ***stenosis of extracranial carotid arteries without a history of ipsilateral ischemic stroke or transient ischemic attack.*** The estimated *prevalence of severe aCAS (≥70%)* increases with age and ranges from *0.1 to 3.1%*[1] with a population-attributable stroke risk of 0.7%.[2]

In 10 to 15% of cases, asymptomatic carotid stenosis (>50%) is the underlying etiology of the ischemic stroke.[3] For asymptomatic carotid stenosis, there are choices for medical therapy and revascularization surgeries, such as carotid endarterectomy (CEA) and carotid artery stenting (CAS). But unlike symptomatic stenosis, the optimal treatment for asymptomatic carotid stenosis is still up for debate.

First, studies on asymptomatic carotid stenosis have shown inconsistent results. Asymptomatic carotid stenosis therapy recommendations abound; however, they differ greatly from one another.[4] We still do not know how many individuals with asymptomatic carotid stenosis require therapy, or which revascularization technique—CEA or CAS—is optimal.

Second, the results of carotid stenosis patients afflicted with atherosclerosis have been steadily improving thanks to new developments in best medical therapy (BMT).[5] Ipsilateral ischemic stroke due to carotid stenosis used to occur at a rate of approximately 2% annually, but that the rate has dropped to less than 1% annually in the last 20 years. Revascularization therapy for asymptomatic carotid stenosis may have less relative efficacy as a consequence of such an improvement.[6,7] Third, CAS is currently more commonly performed than CEA in several countries, even though CEA was originally suggested for revascularization of asymptomatic carotid stenosis.[5,8–10]

Methods to Quantify ICA Stenosis

There are a number of well-established ways to determine the degree of internal carotid artery (ICA) stenosis prior to revascularization in clinical practice around the world.

In North America, the normal distal ICA is typically used as the denominator in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), whereas in Europe, the estimated width of the original artery at the site of maximal narrowing (ECST) is typically used.[11–13] The common carotid (CC) method is also used by a number of institutions because of how much more reproducible it is. One common denominator among all methods is the proximal common carotid artery (CCA).[14,15] These risk categorization methods are all equally reliable and produce similar outcomes (**Fig. 13.1**).[14]

"It is well understood that both the ECST and CC methods result in a higher percentage stenosis compared with NASCET," considering that the distal ICA, the denominator utilized in NASCET, is often smaller than the proximal ICA or CCA. Regrettably, identifying the most anatomically accurate measurement method is next to impossible without a gold standard.

"With regards to intramodality correlation and agreement, all three methods

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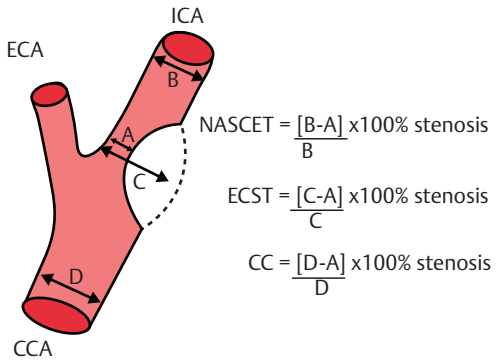

A= Luminal diameter at the site of maximal narrowing

B = Diameter of normal distal ICA beyond the bulb where the artery walls are parallel

C = Diameter of estimated original width of the ICA at the site of maximal narrowing

D = Diameter of normal CCA proximal to the bulb where artery walls are parallel.

Fig. 13.1 Diagram demonstrating different methods used to quantify internal carotid artery (ICA) stenosis.[16]

overall performed similarly." At our clinic, the NASCET approach is widely used for everyday patient care. Complete occlusion, severe (70% to 99%), moderate (50% to 69%), and mild stenosis were the four categories used by the NASCET approach.

The equation demonstrated below[17] has been used to determine the link between the degree of narrowing based on the NASCET definition and the ECST definition.

% Stenosis (by ECST) = 0.6 × % Stenosis (by NASCET) + 40%

Risk Factors for Carotid Stenosis

Factors that increase the risk of carotid artery disease include[18]:

- **High blood pressure:** It reduces artery wall strength, making them more vulnerable to injury.
- **Tobacco use:** Arterial intima can get inflamed by nicotine. Both the heart rate and blood pressure are elevated when one smokes.
- **Diabetes:** It reduces fat processing abilities, which increases the risk of hypertension and atherosclerosis.

"Smoking, diabetes, and hypertension were significant risk factors for increased carotid intima–media thickness and carotid plaque."[19]

- **High blood fat levels:** Plaques are made easier to form when triglyceride (TG) and low-density lipoprotein (LDL) cholesterol levels are high.
- **Family history:** If atherosclerosis or coronary artery disease runs in one's family, the likelihood of developing carotid artery disease is increased.
- **Age:** As we become older, our arteries stiffen up and become more prone to injury.
- **Obesity:** It raises the risk of diabetes, atherosclerosis, and hypertension.
- **Sleep apnea:** The risk of stroke may be increased if you experience spells of not breathing at night.
- **Lack of exercise:** It causes diabetes, obesity, and hypertension.

Carotid artery disease can lead to stroke through:
Hypoperfusion, embolus, or thrombus (thromboembolism).

Current Evidence

Surgical Intervention—Carotid Endarterectomy (CEA)

Two landmark randomized controlled trials **(RCTs) ACAS and ACST-1** compared **CEA plus BMT with BMT alone** in patients with **aCAS (≥60% stenosis)** (**Table 13.1**).

ACAS found a *5-year risk of ipsilateral stroke, perioperative stroke, or death of* ***5.1%***

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Table 13.1 Landmark randomized controlled trials for carotid endarterectomy

Trial	Recruitment period	Number of patients	Population	Perioperative risk of any stroke and death	Risk of any stroke (including perioperative) and death	Number needed to treat
ACAS	1987–1993	1662	Asymptomatic (never symptomatic)	2.3%	5 years: 5.1% (CEA) vs. 11.0% (BMT)	17
ACST-1	1993––2003	3120	Asymptomatic (6 months or longer)	3.1%	5 years: 6.4% (CEA) vs. 11.8% (BMT)	19

Abbreviations: BMT, best medical therapy; CEA, carotid endarterectomy.

versus 11.0% in the CEA versus BMT arm ($p < 0.004$).[20] **ACST-1** found a *5-year risk of stroke and perioperative events of* ***6.4% versus 11.8% in the CEA versus BMT arm*** ($p < 0.0001$).[21] As such, the 2011 AHA guidelines along with 13 other societal ***guidelines recommended CEA in patients with aCAS with ≥70% stenosis if perioperative stroke, myocardial infarction (MI), and death rates were low.***[22]

New, more stringent, data-driven guidelines were introduced to BMT following the completion of these trials; these guidelines are detailed below. A 10-year follow-up of the ACST-1 experiment found that the number of patients needed to treat for CEA increased from 19 to 22 during the first and second 5-year periods, and that the proportion of patients taking antihypertensives and lipid lowering medication increased from 53% and 10% to 88% and 81% respectively. The risk of stroke in the medical arm reduced throughout this period.[23]

A number of trials are currently re-examining this subject, including the Carotid Revascularisation and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2), which sparked disagreement over the relative merits of modern BMT and CEA.[24]

Carotid Artery Stenting (CAS)

The use of carotid stenting and subsequent head-to-head comparison trials followed CEA's establishment as the gold standard for aCAS revascularization. These include the **CREST** trial, which compares carotid revascularization endarterectomy with stenting, the **ACT-I** trial, which compares stents with surgery for asymptomatic carotid stenosis, and the **ACST-2** trial, which is the second iteration of the **ACT-I**[25–28] (**Table 13.2**).

Results from a pooled analysis of three **RCTs (SAPPHIRE, CREST-1, and ACT-I)** showed no significant difference in the ***composite endpoint*** of periprocedural stroke, mortality, MI, or long-term ipsilateral strokes across therapies (Relative risk [RR] 0.92; 95% confidence interval [CI] 0.70 to 1.21).[29]

Results from the most recent **ACST-2 study** showed the "***same level of effectiveness and safety. At the 5-year mark, the Kaplan-Meier estimates for non-procedural stroke were 2.5% for fatal or debilitating stroke in the CAS group and 5.3% vs. 4.5% for any stroke in the CEA group (RR 1.16; 95% CI 0.86 to 1.57).***"[28] In general, the results of both treatments were comparable when looking at the accumulated evidence.

In response to the progress in BMT after completion of early CEA and select CAS studies, the SPACE-2 trial was designed as a three-arm comparison of BMT, CEA, and CAS.[18] Unfortunately, due to terrible enrolment, SPACE-2 was halted after 513 patients (rather than the intended 3550)—which is a disappointing news. There was no statistically significant difference in the 1-year incidence

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Table 13.2 Landmark randomized controlled trials for carotid artery stenting

Trial	Recruitment period	Number of patients	Population	Perioperative risk of any stroke and death	Risk of any stroke (including perioperative) and death	Relative risk
SAPPHIRE	2000–2002	334	Symptomatic (97)/asymptomatic (237)	5.5% (CAS) vs. 8.4% (CEA), $p = 0.36$‡	3 years: 21.4% (CAS) vs. 29.2% (CEA)†	0.74 (95% CI 0.47 to 1.14)
CREST-1	2005–2008	2502	Symptomatic (1321)/asymptomatic (1181)	2.5% (CAS) vs. 1.4% (CEA), $p = 0.15$	10 years: 11.8% (CAS) vs. 9.9% (CEA)†	1.10 (95% CI 0.83 to 1.44)
ACT-1	2005–2013	1453	Asymptomatic	2.9% (CAS) vs. 1.7% (CEA), $p = 0.33$	5 years: 3.8% (CAS) vs. 3.3% (CEA)†	1.14 (95% CI 0.61 to 2.15)
ACST-2	2008–2020	3625	Asymptomatic	3.7% (CAS) vs. 2.7% (CEA), $p = 0.12$	5 years: 5.3% (CAS) vs. 4.5% (CEA)	1.11 (95% CI 0.91 to 1.32)

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval.
‡The value represents numerical risk combined for both asymptomatic and symptomatic populations.
†These trials include the incidence of myocardial infarction in addition to risk of any stroke and death.

of ipsilateral stroke in 2.0% of CEA, 3.0% of CAS, and 0.9% of BMT, according to the 1-year interim study.[30,31] As mentioned previously, there is still ongoing dispute about the significance of CAS and CEA in modern BMT, and studies are actively seeking participants to shed light on this matter.

Best Medical Therapy (BMT)

BMT has come a long way from its vague beginnings in the aCAS trials; today, it includes a wide range of antiplatelet regimens, lipid-lowering medications, strict monitoring of hyperglycemia and blood pressure, and lifestyle changes. These advancements have reduced the risk of stroke in individuals with aCAS who undergo BMT, rendering previous landmark intervention trials less relevant. The medicine arm of the 1995 ACAS study had an ipsilateral stroke risk of 11% after 5 years, but the ACST-1 trial had an ipsilateral risk of 3.6%.[20,21]

In a systematic review from 1985 to 2007, the risk of an ipsilateral stroke decreased dramatically from 2.8 to 1.4% in 11 trials involving 3,724 individuals with aCAS who underwent BMT. The prevalence of high total cholesterol was found to be 32% higher, antiplatelet use was 22% higher, and current smoking status was 14% lower, all of which were connected with this.[31,32] Data points to the idea that the "rate of stroke with BMT is quickly approximating 1% per year."[32–34] In parallel, CAS and CEA have become safer, with declining perioperative risk approaching 1%.[35]

Limitations of BMT encompass its reliance on compliance for longevity, an area that has been extensively studied. Indeed, just 34% of participants in the current **CREST-2** trial really follow their hypertension treatment plans according to the guidelines.[36] In general, the best way to handle aCAS is still not clear. As we wait for CREST-2 to finish, "it seems most logical to select patients with aCAS who are deemed to have a higher risk of developing stroke despite receiving fully optimized BMT" (**Table 13.3**).

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Table 13.3 Medical therapy used in prior landmark randomized controlled trials versus contemporary best medical therapy[37–41]

	Definition of BMT in prior RCTs		Modern BMT
1980s	**VACS** "Aspirin 650 mg twice/day or 325 mg/day if unable to tolerate"	**2008**	"Lipid-lowering[74,75]: atorvastatin 40–80 mg or rosuvastatin 20–40 mg (SPARCL) ± ezetimibe with target LDL<70 mg/dL. Despite maximal statin and ezetimibe therapy if LDL >70 mg/dL, PCSK9 inhibitor can be used."
1990s	**ACAS** "Aspirin 325 mg/day. 'Discussion' of hypertension, diabetes mellitus, abnormal lipid levels, excessive alcohol, and tobacco use"	**2011**	"Blood pressure.[75] Target BP <130/80 mm Hg or <140/90 mm Hg (previously <140/90 mm Hg alone)"
2000s	**ACST-1** "Antiplatelet, antihypertensive, lipid-lowering therapy. Lipid-lowering drugs: 10%–>81%; BP therapy: 53%–>88%; notable increase between 1993 and 2007.	**2018** **2020**	**Antiplatelet:** **2018: POINT trial** showed the reduction in recurrent ischemic events at 90 days when patients with minor stroke or high-risk TIA were treated with aspirin 50–325 mg and clopidogrel 75 mg followed by initial loading dose of aspirin 50–325 mg and clopidogrel 600 mg. **2020: THALEz trial** showed the reduction in recurrent ischemic events at 90 days when patients with a mild–moderate acute non-cardioembolic stroke or with a high risk of a TIA were treated with aspirin 75–100 mg and ticagrelor 90 mg twice per day followed by initial loading dose of aspirin 300–325 mg and ticagrelor 180 mg.
		2021	**Rest as per 2021 AHA guideline:** **Diabetes mellitus:** HbA1c ≤7 (multidimensional care: nutritional education, lifestyle counseling, medication). **Smoking cessation:** Counseling with or without drug therapy (nicotine replacement, bupropion, or varenicline). **Obesity:** Behavioral lifestyle modification program. **Diet:** Mediterranean diet. **Obstructive sleep apnea:** Treatment with positive airway pressure.

Abbreviations: BMT, best medical therapy; LDL, low-density lipoprotein; RCTs, randomized controlled trials; TIA, transient ischemic attack.

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Clinical Risk Assessment

Clinical features of patients with aCAS may play a role in helping with therapeutic decision-making and risk assessment for future ischemic episodes. With 1,121 patients treated with BMT for aCAS, the Asymptomatic Carotid Stenosis and Stroke Risk Study (ACSRS) is the most prospective clinico-radiographic correlation study to date.[42]

Factors associated with higher stroke risk included[42]:

- Increase in age by 10 years (HR 1.42; 95% CI 1.00 to 2.02).
- Increase in serum creatinine by 20% (HR 1.28; 95% CI 1.09 to 1.50).
- History of contralateral ischemia (HR 3.03; 95% CI 1.77 to 5.20).
- Increase in systolic blood pressure by 10 units (HR 1.11; 95% CI 1.07 to 1.22).
- History of smoking of 10 or more pack-years (HR 1.65; 95% CI 1.16 to 2.34).

Although ACSRS has shown an increased risk of stroke in the presence of contralateral ischemic events, surgical revascularization is ineffective for patients with significant stenosis or carotid artery occlusion on the opposite side.[43–45] The ACAS study found that patients whose occlusions occurred on the opposite side of their bodies fared worse. Within 5 years, 3.5% of the patients in the BMT group and 5.5% of the patients in the CEA group experienced ischemia episodes.[43]

Imaging Risk Factors

In the lack of definitive universal proof, imaging features that can forecast a higher risk of ischemic stroke have been identified and show promise in patient selection. A recent meta-analysis of 64 studies involving 20,751 patients with carotid stenosis found a 26.5% incidence of high-risk features with a correlative increase in the rate of ipsilateral ischemic stroke (4.3 vs. 1.2 events per 100 person-years; odds ratio [OR] 3.0; 95% CI 2.1 to 4.3).[46]

Hypoperfusion and thromboembolism are the principal pathophysiological causes of stroke in carotid stenosis; these features help identify individuals at risk of developing these conditions. The worsening of stenosis and the failure of collaterals lead to hypoperfusion. Plaque rupture exposes the necrotic core material, which is highly thrombogenic, and can cause thromboembolism.[47–49] Particularly helpful are imaging features that can identify the beginning of the rupture process or the rupture itself.

In the process of plaque evolution, the progression of an atheroma from its initial development to a lipid-rich necrotic core, neovascularization, intraplaque hemorrhage (IPH), fibrous cap weakening, and eventual rupture is a complicated process.

Transcranial Doppler (TCD)

Microemboli Detection

Transcranial Doppler (TCD) high intensity transient signals (TCD-HITS) symbolize a microembolic occurrence.[50] Using well-established methodology, TCD-HITS has been successfully performed for decades, insonating about 90% of patients. Most recently, the Asymptomatic Carotid Emboli Study (ACES) demonstrated its predictive importance for future strokes in patients with aCAS.[51] It is the largest and most comprehensive study of its kind.

In this ACES multicenter prospective observational study of 467 patients with aCAS (≥60% stenosis), the incidence of at least one HITS was 16.5%. An ipsilateral stroke was six times more likely to occur over the 2-year follow-up period (HR 5.90, $p < 0.006$). Including five more observational studies totaling 1,114 participants, a new contemporaneous meta-analysis found an ipsilateral stroke risk nearly seven times higher (OR 6.63, $p = 0.001$).[52]

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The TCD-HITS measure is another potential indicator of therapy effectiveness. This prospective study included 468 individuals with 60% or more asymptomatic carotid stenosis, and the prevalence of HITS dropped from 12.6% in patients recruited before 2003 to 3.7% between 2003 and 2007. The second group took a lot more statins, antihypertensives, and antiplatelet medication than the first.[53]

Post-CEA studies also demonstrated near-complete disappearance of HITS in the following days after CEA.[54,55] The technology's 10% insonation failure rate and reliance on operators are its main drawbacks; yet, robotic TCD shows potential in eliminating operator dependence.[56] In general, TCD has a high predictive value, is widely available, does not involve radiation, and is cost-effective.

Cerebrovascular Reactivity

Upstream of a narrowed artery is where the vascular reserve is measured by cerebrovascular reactivity (CVR). In order to restore normal blood flow, circulations subjected to chronic hypoperfusion will widen the vasculature downstream. A chronically compensated circulation is maximally dilated and does not react to subsequent vasodilatory stimuli, making hypoperfusion infarcts due to carotid stenosis conceivable.

TCD studies measure the middle cerebral artery mean flow velocities (MFVs) before and after a vasodilatory challenge, such as holding one's breath or inhaling carbon dioxide (CO_2), is provided; this is one of the most common ways to determine CVR. People whose CVR is weak will have TCD velocities that are identical before and after the vasodilatory challenge, in contrast to patients whose CVR is normal, whose velocities increase after a challenge.

In a meta-analysis of 13 studies involving 991 participants, stroke risk was four times higher in patients with CVR impairment (OR 3.96; 95% CI 2.60 to 6.04). This included both asymptomatic and symptomatic carotid stenosis patients.[57] Among these 13 trials, 3 involving 152 patients found a fourfold increase in the risk of stroke (OR 4.00; 95% CI 1.27 to 12.60) in the aCAS group. The inability to screen for the less common low perfusion type ischemia and the inconsistent definition of poor CVR are two of its limitations.

Carotid Ultrasound

Plaque Echolucency

Plaques with lipid-rich necrotic cores or IPH appear echolucent on carotid ultrasound.[58] Although qualitative evaluations have their place, standardization is crucial due to the non-standardization of picture acquisition. Such criteria are provided by a number of quantitative methods, such as the Gray-Scale median and the Gray-Weale.[59]

A meta-analysis of seven studies involving 7,557 patients with aCAS and mean follow-up of 3 years found an increased risk of ipsilateral stroke across all stenosis severities in subjects with echolucent plaques compared with echogenic (RR 2.31; 95% CI 1.58 to 3.39; $p < 0.001$).[60] These findings were *reproduced in a post hoc analysis of the ACST-1 trial medical arm, demonstrating higher 5-year ipsilateral stroke risk in patients with echolucent plaque* (HR 2.52; 95% CI 1.20 to 5.25; $p = 0.014$).[61] In the ACES, the combination of plaque echolucency and TCD-HITS was associated with a more than 10-fold increased risk of ischemic stroke (HR 10.61; 95% CI 2.98 to 37.82).[52]

The distribution of the echolucency within the plaque additionally aid in forecasting. There is a greater danger associated with a juxtaluminal position compared to a central one.[62] As a result, the Juxtaluminal Black Area (JBA) was born, which stands for newly formed thrombotic components on the surface of the plaque without a fibrous cap covering them.[63] On the histopathological side, this is associated with a thinning or torn cap, bleeding within

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the plaque, thrombus on the surface, and inflammation of the cap. An independent predictor of ischemic events, as demonstrated by computer-assisted quantification, is a JBA of 8 mm^2 or more.[64]

The ACSRS study showed comparable outcomes, with a yearly stroke rate of 0.4% in JBA <4 mm^2 and 3.2% in >8 mm^2, respectively.[65] Despite this feature's shortcomings—namely, heterogeneity in reporting and inter-reader variability—it can be easily implemented in practice due to its widespread availability and inexpensive cost.

Progression of Stenosis

Treatment selections are often based on the severity of carotid stenosis, which has long been associated with stroke risk. The ACSRS study found that the yearly risk of stroke increased in a linear fashion with the severity of the stenosis (0.8% for 50–69%, 1.4% for 70–89%, and 2.4% for 90–99%).[66] Additionally, findings imply that it may be linked to stroke risk; hence, monitoring the advancement of stenosis over time is a common practice for treatment decision-making. Asymptomatic carotid stenosis has a progression incidence of 9.0 to 29.1%.[67,68]

The ACSRS study demonstrated that there was no cumulative ipsilateral stroke risk in patients whose stenosis had regressed after 8 years, 9% in those whose stenosis had remained stable, and 16% in those whose stenosis had progressed (RR 1.92; 95% CI 1.14 to 3.25).[69] This study ranked the stenoses from 50 to 59%, 60 to 69%, 70 to 79%, 80 to 89%, 90 to 95%, and 96 to 99%. It was seen as a step up to go up a class.

Similarly, another study that looked at intermediate asymptomatic stenosis (50–69%) over a median follow-up period of 3.6 years found that 8.5% of nonprogressors and 13.7% of progressors experienced ipsilateral ischemic episodes, respectively (RR 1.62; 95% CI 1.09 to 2.41).[67]

Additionally, despite the administration of antiplatelet and lipid-lowering medications in over 85% of patients, progression was observed in 29.1% of cases. Although stenosis progression is practically always tracked, its predictive value is sometimes disregarded. Several methods exist for keeping tabs on this, including ultrasonography, computed tomography (CT) angiography (CTA), and magnetic resonance angiography (MRA), the latter of which has the lowest resolution.

Plaque Ulceration

A previous plaque rupture exposes the necrotic core, which can be a source of thromboembolic events, and any intimal defect bigger than 1 mm shows this.[70,71] About 13% of aCAS cases have plaque ulceration. CTA and MRA both have sensitivity and specificity levels above 90%, even though DSA is considered the gold standard.[72,73] On the other hand, carotid ultrasonography has a much lower sensitivity of only around 30%.[74,75]

In a study that compared individuals with aCAS who had many ulcerations (1.4% vs. 7.1%, $p < 0.049$) to those without ulcers, the incidence of ipsilateral ischemic strokes after 3 years was shown to be higher in the former group.[76]

Plaque ulceration as a predictor for future ipsilateral ischemic episodes in patients with aCAS requires further confirmation because of the scarcity of studies utilizing this method. Nevertheless, its value should not be undervalued because, according to high-quality research, people with symptomatic CAS who develop plaque ulceration are more likely to suffer an ipsilateral stroke.[71,77]

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MRI: Intraplaque Hemorrhage (IPH)

It is well known that IPH speeds up the process of plaque formation and rupture. It is possible to detect IPH using a variety of magnetic resonance imaging (MRI) methods, including T1-weighted imaging, fat-suppressed two-dimensional or three-dimensional imaging, time-of-flight MRA imaging, and magnetization-prepared fast acquisition gradient-echo imaging.[78–80] The more popular clinical T1-weighted scans can identify IPH with an 80% sensitivity and a 97% specificity.[81] An IPH incidence of 29.4% in aCAS was found in a meta-analysis of seven trials using T1-weighted MRI during the 30-month follow-up period. Compared to those with IPH, those without it had a 7.9% (95% CI 1.3 to 47.6) higher annual risk of ipsilateral stroke.[82] Although there is certainly promise in rapidly developing technology, there are also downsides, such as the tendency to exaggerate the severity of nonsevere carotid stenosis[83] and the higher expenses linked with the need for specific sequences.

Ipsilateral Silent Brain Infarction (SBI)

When a stenotic carotid artery is located downstream of a patient's ***asymptomatic brain; this condition is known as a silent brain infarction (SBI).*** The ACSRS found that 18% of patients with an ipsilateral SBI had it during an average follow-up of 44.6 months. Subjects without SBI were 1.0% more likely to have a subsequent ipsilateral ischemic stroke, but those with SBI were 3.6% more likely ($p = 0.002$).[66] Due to their small size and location, these lesions typically do not cause any symptoms. However, when they progress, they can increase the likelihood of developing vascular dementia and cognitive impairment.[84] Lack of unanimity and inadequate specificity are the limitations. But SBI is often gleaned from first imaging assessments of aCAS patients; thus, it is a readily available predictor.

Recent Studies for Asymptomatic Carotid Stenosis

Stroke Risk with Degree of Asymptomatic Carotid Stenosis (aCAS)

Recent studies by **Howard et al (2021),**[85] **Chang et al (2023),**[86] **and Poorthuis et al (2023)**[87] looked at individuals with aCAS and discovered that the risk of ipsilateral stroke decreased by 24% for every 5 years of enrolment. Ipsilateral stroke was less common in patients who had aCAS and had intermediate (50–69%) stenosis. The risk of stroke was more than 2.5 times greater for patients with 80 to 99% aCAS and more than 2 times higher for those with 70 to 99% aCAS when compared to patients with a CAS of 50 to 69%[4] (**Table 13.4**).

Comparison of Outcomes Between CEA and CAS in Asymptomatic Carotid Patients

In recent studies by **Wang et al (2022)**[88] **and Saratzis and Naylor (2022)**[89] **comparing** CEA and CAS in aCAS patients, the results showed no significant change in the incidence of perioperative stroke, MI, and death. The risk of perioperative and nondisabling strokes was higher with trans femoral carotid artery stenting (TF-CAS) compared to CEA.[90]

SPACE-2 (Stent-Protected Angioplasty vs Carotid Endarterectomy) (2022): The purpose of this clinical trial was to compare three

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Table 13.4 Stroke risk with degree of asymptomatic carotid stenosis (aCAS)

Study	Year	Study design	Outcome
Howard et al[85]	2021	**Risk of stroke in relation to degree of aCAS** (cohort study, systematic review, and meta-analysis)	Patients with **70–99% aCAS had a >2-fold higher risk of stroke** compared with patients with 50–69% aCAS (OR, 2.1; 95% CI, 1.7–2.5; P < 0.0001) Patients with **80–99% aCAS had a 2.5-fold higher risk of stroke** compared with those with 50–69% aCAS (OR, 2.5; 95% CI, 1.8–3.5; P < 0.0001)
Chang et al[86]	2023	**Comparison of stroke risk with CEA vs. BMT** for patients with 70–99% aCAS	Patients **undergoing CEA had a lower risk of stroke compared with those receiving only BMT starting from year 2** (RD, 1.1%; 95% CI, 0.5–1.6%), which persisted through year 8 (RD, 2.6%; 95% CI, 0.3–4.8%).
Poorthuis et al[87]	2023	**Stroke risk in patients with aCAS treated with BMT**	The **incidence of ipsilateral ischemic stroke decreased by 24% with every 5 years of recruitment** (IRR, 0.76; 95% CI, 0.73–0.78; 64 studies). The incidence rates of ipsilateral ischemic stroke were lower in female patients (IRR, 0.74; 95% CI, 0.63–0.87; 5 studies) and in individuals with moderate (50–69%) vs. severe (70–99%) stenosis (IRR, 0.45; 95% CI, 0.39–0.52; 21 studies).

Abbreviations: BMT, best medical therapy; CEA, carotid endarterectomy; CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; RD, risk difference.

different treatment modalities for patients with aCAS: TF-CAS plus BMT, CEA plus BMT, and BMT alone. There was no significant difference in the 30-day and 5-year cumulative incidence of stroke, death, or ipsilateral ischemic stroke between the CEA + BMT, TF-CAS + BMT, and BMT alone groups. The trial was terminated too soon due to slow patient enrolment.

Keyhani et al (2022) compared the 5-year stroke rates in aCAS patients treated with TF-CAS to those treated with BMT alone in a retrospective analysis. There was no change in the ***5-year risk of fatal and nonfatal stroke between TF-CAS and BMT alone, according to the results***[91] **(Table 13.5).**

Studies Evaluating Cognitive Function in Patients with Asymptomatic Carotid Stenosis

Systematic review by **Paraskevas et al (2021, 2023)**[92,93,94] **and SMART-MR (Second Manifestation of ARTerial Disease Magnetic Resonance Study)**[94] found that aCAS was associated with at least one cognitive impairment test, indicating that patients with aCAS may be experiencing cognitive decline. Mechanisms such as silent cerebral embolization and cerebral hypoperfusion were involved. The studies also hinted that memory and executive functioning were worse in people with low-grade aCAS (**Table 13.6**).

Conclusion

Many national and international standards have been produced about the treatment of individuals with aCAS, but the issue remains highly controversial. Advances in BMT have led to a decline in the incidence of stroke and a smaller relative benefit from carotid revascularization procedures in patients with aCAS. The risk of stroke is further reduced when several vascular risk factors, including LDL cholesterol, systolic blood pressure,

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Table 13.5 Comparison of outcomes between carotid endarterectomy (CEA) and carotid artery stenting (CAS) in asymptomatic carotid patients

Study	Year	Study design	Outcome
Wang et al[88]	2022	Comparison of TF-CAS vs. CEA outcomes based on RCT results	**No difference in perioperative stroke, MI, and death** between the two procedures (OR, 1.13; 95% CI, 0.87–1.47; *P* = 0.37; I2 = 0%). **TF-CAS was associated with a higher risk of any perioperative stroke** (OR, 1.62; 95% CI, 1.16–1.24; *P* = 0.004; I^2 = 0%) and nondisabling stroke (OR, 1.81; 95% CI, 1.23–2.65; *P* = 0.003; I^2 = 0%) compared with CEA.
Saratzis and Naylor[89]	2022	Comparison of TF-CAS vs. CEA outcomes based on RCT results	**The composite outcome of death/any stroke/MI was not significantly different** between TF-CAS and CEA (OR, 1.19; 95% CI, 0.89–1.59; *P* = 0.89). **TF-CAS was associated with worse outcomes compared with CEA in patients with aCAS when stroke alone** (OR, 1.61; 95% CI, 1.18–2.21; *P* = 0.003) **or death and stroke** (OR, 1.47; 95% CI, 1.09–1.99; *P* = 0.11) **were considered.**
SPACE-2[90]	2022	RCT comparing outcomes between TF-CAS + BMT vs. CEA + BMT vs. BMT alone for aCAS patients	The **cumulative incidence of any stroke or death from any cause within 30 days and any ipsilateral ischemic stroke within 5 years was similar** for **CEA + BMT, TF-CAS + BMT, and BMT alone** (2.5% vs. 4.4% vs. 3.1%, respectively. HR for CEA + BMT vs. BMT alone: 0.93; 95% CI, 0.22–3.91; *P* = 0.93. HR for TF-CAS + BMT vs. BMT alone: 1.55; 95% CI, 0.41–5.85; *P* = 0.52.
Keyhani et al[91]	2022	Retrospective comparison of 5-year stroke rates after TF-CAS vs. BMT alone in aCAS patients	The **5-year risk of fatal and nonfatal stroke was similar between TF-CAS and BMT alone** (6.9% vs. 7.1%, respectively; risk difference: 0.1; 95% CI, −2.6% to 2.7%; *P* = not significant).

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; TF-CAS, trans femoral carotid artery stenting.

triglycerides, and HDL cholesterol, are well-managed.

An increased risk of future strokes persists in certain subgroups of aCAS patients. These include patients with very narrow blood vessels (80–99%), microemboli found on TCD, plaque echolucency on Duplex ultrasound, silent embolic infarcts on brain CT/MRI angiography, decreased cerebrovascular reserve, larger juxtaluminal hypoechoic area, advanced atherosclerotic stenosis, carotid plaque ulceration, and intraplaque hemorrhage on MRI. A preventive carotid intervention is probably necessary for these persons with aCAS to minimize the high risk of future stroke.

To better select patients for invasive treatment modalities other than BMT, current or future stroke risk prediction tools should be further developed. Research on the potential effects of carotid revascularization treatments on cognitive function decline and the role of aCAS in this decline should be prioritized in the future.

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Table 13.6 Studies evaluating cognitive function in patients with asymptomatic carotid stenosis

Study	Year	Study design	Outcome
Paraskevas et al[92]	2021	**Systematic review** (*n* = 35 studies) evaluating cognitive function in aCAS patients	Overall, 33 of 35 studies demonstrated **an association between aCAS with >/= 1 test of cognitive impairment.** The main mechanism involved was impaired cerebrovascular reserve.
Paraskevas et al[93]	2023	**Systematic review** (*n* = 49 studies) evaluating cognitive function in aCAS patients	Nearly all the studies suggested an **association between aCAS and progressive cognitive decline.** The mechanisms involved included cerebral hypoperfusion and silent cerebral embolization.
SMART-MR[94] **(Second Manifestations of ARTerial Disease-Magnetic Resonance study)**	2023	**Comparison** of cognitive function in patients with vs. without low-grade (149%) aCAS	**Low-grade aCAS was associated with a greater decline in executive function** (estimate: 0.02; 95% CI, −0.031 to 0.01; $P < 0.001$) and **memory** (estimate: 0.012; 95% CI, –0.02 to 0.001; $P = 0.032$).

Abbreviations: aCAS, asymptomatic carotid artery stenosis; CI, confidence interval.

References

1. de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41(6):1294–1297
2. Goldstein LB. Screening for asymptomatic carotid artery stenosis: caveat emptor. Ann Intern Med 2014;161(5):370–371
3. Naylor AR, Ricco JB, de Borst GJ, et al; Esvs Guidelines Committee; Esvs Guideline Reviewers. Editor's choice—management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55(1):3–81
4. Paraskevas KI, Mikhailidis DP, Antignani PL, et al. Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement. J Stroke Cerebrovasc Dis 2022;31(1):106182
5. Hackam DG. Optimal medical management of asymptomatic carotid stenosis. Stroke 2021; 52(6):2191–2198
6. Messas E, Goudot G, Halliday A, et al. Management of carotid stenosis for primary and secondary prevention of stroke: state-of-the-art 2020: a critical review. Eur Heart J Suppl 2020;22(Suppl M):M35–M42
7. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273(18):1421–1428
8. Halliday A. Treatment of asymptomatic carotid artery stenosis. Lancet Neurol 2022;21(10): 858–859
9. White CJ, Brott TG, Gray WA, et al. Carotid artery stenting: JACC state-of-the-art review. J Am Coll Cardiol 2022;80(2):155–170
10. Seo KD, Lee KY, Suh SH. Comparison of long term prognosis between carotid endarterectomy versus stenting; a Korean population-based study using National Insurance data. Neurointervention 2019;14(2):82–90
11. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351(9113):1379–1387
12. Barnett HJ, Taylor DW, Eliasziw M, et al; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate

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or severe stenosis. N Engl J Med 1998;339(20): 1415–1425
13. Rothwell PM, Eliasziw M, Gutnikov SA, et al; Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361(9352):107–116
14. Rothwell PM, Gibson RJ, Slattery J, Warlow CP. Prognostic value and reproducibility of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke 1994;25(12):2440–2444
15. Wardlaw JM, Lewis SC, Humphrey P, Young G, Collie D, Warlow CP. How does the degree of carotid stenosis affect the accuracy and interobserver variability of magnetic resonance angiography? J Neurol Neurosurg Psychiatry 2001;71(2):155–160
16. U-King-Im JM, Trivedi RA, Cross JJ, et al. Measuring carotid stenosis on contrast-enhanced magnetic resonance angiography: diagnostic performance and reproducibility of 3 different methods. Stroke 2004;35(9):2083–2088
17. Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke 1994;25(12): 2435–2439
18. Texakalidis P, Chaitidis N, Giannopoulos S, et al. Carotid revascularization in older adults: a systematic review and meta-analysis. World Neurosurg 2019;126:656–663.e1
19. Song P, Fang Z, Wang H, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health 2020;8(5):e721–e729
20. Walker MD, Marler JR, Goldstein M, et al. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273(18):1421–1428
21. Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363(9420):1491–1502
22. Brott TG, Halperin JL, Abbara S, et al; American College of Cardiology Foundation; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurological Surgeons; Society of Atherosclerosis Imaging and Prevention; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 2011;124(4):489–532
23. Halliday A, Harrison M, Hayter E, et al; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;376(9746):1074–1084
24. Howard VJ, Meschia JF, Lal BK, et al; CREST-2 study investigators. Carotid revascularization and medical management for asymptomatic carotid stenosis: protocol of the CREST-2 clinical trials. Int J Stroke 2017;12(7):770–778
25. Gurm HS, Yadav JS, Fayad P, et al; SAPPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med 2008;358(15):1572–1579
26. Brott TG, Hobson RW II, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363(1):11–23
27. Rosenfield K, Matsumura JS, Chaturvedi S, et al; ACT I Investigators. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med 2016;374(11):1011–1020
28. Halliday A, Bulbulia R, Bonati LH, et al; ACST-2 Collaborative Group. Second asymptomatic

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carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet 2021;398(10305): 1065–1073
29. Moresoli P, Habib B, Reynier P, Secrest MH, Eisenberg MJ, Filion KB. Carotid stenting versus endarterectomy for asymptomatic carotid artery stenosis: a systematic review and meta-analysis. Stroke 2017;48(8):2150–2157
30. Reiff T, Eckstein HH, Mansmann U, et al. Angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy compared to best medical treatment: one-year interim results of SPACE-2. Int J Stroke 2019;15(6):1747493019833017
31. Naylor AR. Asymptomatic carotid artery stenosis: state of the art management. J Cardiovasc Surg (Torino) 2013;54(1, Suppl 1):1–7
32. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40(10):e573–e583
33. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke 2010;41(1):e11–e17
34. den Hartog AG, Achterberg S, Moll FL, et al; SMART Study Group. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. Stroke 2013;44(4):1002–1007
35. Munster AB, Franchini AJ, Qureshi MI, Thapar A, Davies AH. Temporal trends in safety of carotid endarterectomy in asymptomatic patients: systematic review. Neurology 2015;85(4):365–372
36. Haley W, Shawl F, Charles Sternbergh W III, et al. Non-adherence to antihypertensive guidelines in patients with asymptomatic carotid stenosis. J Stroke Cerebrovasc Dis 2021;30(8):105918
37. Hobson RW II, Weiss DG, Fields WS, et al; The Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328(4):221–227
38. Amarenco P, Bogousslavsky J, Callahan A III, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355(6):549–559
39. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/ American Stroke Association. Stroke 2021;52(7): e364–e467
40. Johnston SC, Easton JD, Farrant M, et al; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018;379(3):215–225
41. Johnston SC, Amarenco P, Denison H, et al; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med 2020;383(3):207–217
42. Nicolaides AN, Kakkos SK, Kyriacou E, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. J Vasc Surg 2010;52(6):1486–1496. e1, 5
43. Baker WH, Howard VJ, Howard G, Toole JF; ACAS Investigators. Effect of contralateral occlusion on long-term efficacy of endarterectomy in the asymptomatic carotid atherosclerosis study (ACAS). Stroke 2000;31(10):2330–2334
44. Brewster LP, Beaulieu R, Kasirajan K, et al. Contralateral occlusion is not a clinically important reason for choosing carotid artery stenting for patients with significant carotid artery stenosis. J Vasc Surg 2012;56(5):1291–1294, discussion 1294–1295
45. Patel PB, LaMuraglia GM, Lancaster RT, et al. Severe contralateral carotid stenosis or occlusion does not have an impact on risk of ipsilateral stroke after carotid endarterectomy. J Vasc Surg 2018;67(6):1744–1751
46. Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur M, Shuaib A, Jickling GC. Prevalence of high-risk plaques and risk of stroke in patients with asymptomatic carotid stenosis: a meta-analysis. JAMA Neurol 2020;77(12):1524–1535
47. Mechtouff L, Rascle L, Crespy V, Canet-Soulas E, Nighoghossian N, Millon A. A narrative review of the pathophysiology of ischemic stroke in carotid plaques: a distinction versus a compromise between hemodynamic and embolic mechanism. Ann Transl Med 2021;9(14):1208
48. Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. Stroke 2000;31(3): 774–781

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49. Pessin MS, Hinton RC, Davis KR, et al. Mechanisms of acute carotid stroke. Ann Neurol 1979;6(3): 245–252
50. Markus HS, Brown MM. Differentiation between different pathological cerebral embolic materials using transcranial Doppler in an in vitro model. Stroke 1993;24(1):1–5
51. Ringelstein EB, Droste DW, Babikian VL, et al; International Consensus Group on Microembolus Detection. Consensus on microembolus detection by TCD. Stroke 1998;29(3):725–729
52. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9(7):663–671
53. Spence JD, Coates V, Li H, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol 2010;67(2):180–186
54. Siebler M, Sitzer M, Rose G, Bendfeldt D, Steinmetz H. Silent cerebral embolism caused by neurologically symptomatic high-grade carotid stenosis. Event rates before and after carotid endarterectomy. Brain 1993;116(Pt 5):1005–1015
55. van Zuilen EV, Moll FL, Vermeulen FE, Mauser HW, van Gijn J, Ackerstaff RG. Detection of cerebral microemboli by means of transcranial Doppler monitoring before and after carotid endarterectomy. Stroke 1995;26(2):210–213
56. Rubin MN, Alexandrov AV, Douville C, Rinsky B, Tsivgoulis G. Novel robotic TCD ultrasound with bubbles versus standard care to detect right to left shunt: study methods. J Neuroimaging 2021; 31(5):858–863
57. Gupta A, Chazen JL, Hartman M, et al. Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. Stroke 2012;43(11): 2884–2891
58. Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. J Cardiovasc Surg (Torino) 1988;29(6):676–681
59. Grønholdt ML, Wiebe BM, Laursen H, Nielsen TG, Schroeder TV, Sillesen H. Lipid-rich carotid artery plaques appear echolucent on ultrasound B-mode images and may be associated with intraplaque haemorrhage. Eur J Vasc Endovasc Surg 1997;14(6):439–445
60. Gupta A, Kesavabhotla K, Baradaran H, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke 2015;46(1):91–97
61. Huibers A, de Borst GJ, Bulbulia R, Pan H, Halliday A; ACST-1 collaborative group. Plaque echolucency and the risk of ischaemic stroke in patients with asymptomatic carotid stenosis within the first Asymptomatic Carotid Surgery Trial (ACST-1). Eur J Vasc Endovasc Surg 2016;51(5):616–621
62. Pedro LM, Fernandes e Fernandes J, Pedro MM, et al. Ultrasonographic risk score of carotid plaques. Eur J Vasc Endovasc Surg 2002;24(6):492–498
63. Kampschulte A, Ferguson MS, Kerwin WS, et al. Differentiation of intraplaque versus juxtaluminal hemorrhage/thrombus in advanced human carotid atherosclerotic lesions by in vivo magnetic resonance imaging. Circulation 2004; 110(20):3239–3244
64. Salem MK, Bown MJ, Sayers RD, et al. Identification of patients with a histologically unstable carotid plaque using ultrasonic plaque image analysis. Eur J Vasc Endovasc Surg 2014;48(2):118–125
65. Kakkos SK, Griffin MB, Nicolaides AN, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. J Vasc Surg 2013;57(3): 609–618.e1, discussion 617–618
66. Kakkos SK, Sabetai M, Tegos T, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. J Vasc Surg 2009;49(4):902–909
67. Conrad MF, Boulom V, Mukhopadhyay S, Garg A, Patel VI, Cambria RP. Progression of asymptomatic carotid stenosis despite optimal medical therapy. J Vasc Surg 2013;58(1):128–35.e1
68. Sabeti S, Schlager O, Exner M, et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. Stroke 2007; 38(11):2887–2894
69. Kakkos SK, Nicolaides AN, Charalambous I, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Predictors and clinical significance of progression or regression

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of asymptomatic carotid stenosis. J Vasc Surg 2014;59(4):956–967.e1
70. Sitzer M, Müller W, Siebler M, et al. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke 1995; 26(7):1231–1233
71. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. Stroke 1994;25(2):304–308
72. den Hartog AG, Bovens SM, Koning W, et al. Current status of clinical magnetic resonance imaging for plaque characterisation in patients with carotid artery stenosis. Eur J Vasc Endovasc Surg 2013;45(1):7–21
73. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. CT and ultrasound in the study of ulcerated carotid plaque compared with surgical results: potentialities and advantages of multidetector row CT angiography. AJNR Am J Neuroradiol 2007;28(6):1061–1066
74. Saba L, Yuan C, Hatsukami TS, et al; Vessel Wall Imaging Study Group of the American Society of Neuroradiology. Carotid artery wall imaging: perspective and guidelines from the ASNR Vessel Wall Imaging Study Group and expert consensus recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 2018;39(2):E9–E31
75. Brinjikji W, Huston J III, Rabinstein AA, Kim GM, Lerman A, Lanzino G. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. J Neurosurg 2016;124(1):27–42
76. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. Neurology 2011;77(8):744–750
77. Park AE, McCarthy WJ, Pearce WH, Matsumura JS, Yao JS. Carotid plaque morphology correlates with presenting symptomatology. J Vasc Surg 1998;27(5):872–878, discussion 878–879
78. Yim YJ, Choe YH, Ko Y, et al. High signal intensity halo around the carotid artery on maximum intensity projection images of time-of-flight MR angiography: a new sign for intraplaque hemorrhage. J Magn Reson Imaging 2008;27(6):1341–1346
79. Ota H, Yarnykh VL, Ferguson MS, et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. Radiology 2010;254(2):551–563
80. Narumi S, Sasaki M, Natori T, et al. Carotid plaque characterization using 3D T1-weighted MR imaging with histopathologic validation: a comparison with 2D technique. AJNR Am J Neuroradiol 2015;36(4):751–756
81. Cappendijk VC, Cleutjens KBJM, Heeneman S, et al. In vivo detection of hemorrhage in human atherosclerotic plaques with magnetic resonance imaging. J Magn Reson Imaging 2004; 20(1):105–110
82. Schindler A, Schinner R, Altaf N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-analysis of individual patient data. JACC Cardiovasc Imaging 2020;13(2 Pt 1):395–406
83. Nonent M, Ben Salem D, Serfaty J-M, et al. Overestimation of moderate carotid stenosis assessed by both Doppler US and contrast enhanced 3D-MR angiography in the CARMEDAS study. J Neuroradiol 2011;38(3):148–155
84. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215–1222
85. Howard DPJ, Gaziano L, Rothwell PM; Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. Lancet Neurol 2021;20(3):193–202
86. Chang RW, Pimentel N, Tucker LY, et al. A comparative effectiveness study of carotid intervention for long-term stroke prevention in patients with severe asymptomatic stenosis from a large integrated health system. J Vasc Surg 2023;78(5):1239–1247.e4
87. Poorthuis MHF, Solomon Y, Herings RAR, et al. Temporal trends and determinants of stroke risk in patients with medically treated asymptomatic carotid stenosis. Stroke 2023;54(7):1735–1749
88. Wang J, Bai X, Wang T, Dmytriw AA, Patel AB, Jiao L. Carotid stenting versus endarterectomy for asymptomatic carotid artery stenosis: a systematic review and meta-analysis. Stroke 2022;53(10):3047–3054
89. Saratzis A, Naylor R. 30 Day outcomes after carotid interventions: an updated

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meta-analysis of randomised controlled trials in asymptomatic patients. Eur J Vasc Endovasc Surg 2022;63(1):157–158

90. Reiff T, Eckstein HH, Mansmann U, et al; SPACE-2 Investigators. Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial. Lancet Neurol 2022;21(10): 877–888
91. Keyhani S, Cheng EM, Hoggatt K, et al. Comparative effectiveness of carotid stenting to medical therapy among patients with asymptomatic carotid stenosis. Stroke 2022;53(4):1157–1166
92. Paraskevas KI, Faggioli G, Ancetti S, Naylor AR. Editor's choice—asymptomatic carotid stenosis and cognitive impairment: a systematic review. Eur J Vasc Endovasc Surg 2021;61(6):888–899
93. Paraskevas KI, Mikhailidis DP, Spinelli F, et al. Asymptomatic carotid stenosis and cognitive impairment. J Cardiovasc Surg (Torino) 2023; 64(2):167–173
94. Ghaznawi R, Vonk JM, Zwartbol MH, et al; UCC-SMART Study Group. Low-grade carotid artery stenosis is associated with progression of brain atrophy and cognitive decline. The SMART-MR study. J Cereb Blood Flow Metab 2023;43(2):309–318

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14 Asymptomatic Carotid Stenosis—Is Best Medical Management Enough?

Samba Murthy Krishna Mohan Mavuru and P. N. Sylaja

Introduction

Large vessel atherosclerotic disease (LVAD) is responsible for about 25 to 40% of strokes in the Indian population.[1,2] Although intracranial atherosclerosis is more common among Indians compared to Caucasians, and is estimated to contribute about 78.3% of all LVADs, extracranial carotid atherosclerosis is still a major preventable cause of stroke accounting for about 10% of cases.[2]

Traditionally, carotid artery stenosis (CS) of more than 50% is considered the etiology for stroke when infarction occurs in that arterial territory.[3] However, recent advancements have shown high-risk plaques of less than 50% stenosis can be the cause of stroke.[4] CAS is defined as symptomatic if ischemic symptoms have occurred in its territory (ipsilateral eye or cerebral hemisphere) in the last 6 months.[3] Asymptomatic carotid artery stenosis (ACS) is defined as stenosis of extracranial carotid arteries without a history of ipsilateral ischemic stroke or transient ischemic attack.[5] If ischemic events occurred more than 6 months ago in that territory, then it is considered remotely symptomatic CAS.

Natural History of Asymptomatic Carotid Stenosis

Asymptomatic carotid stenosis is associated with an increased risk of stroke and cognitive decline.

Increased Stroke Risk

The pivotal study by the European Carotid Surgery Trialists Collaboration Group in 1995 found an overall 3-year risk of stroke in asymptomatic carotid artery territory is 2.1%, while the risk reached 4.5% in cases with severe stenosis (70–99%).[6] Fatal stroke risk at 3 years was only 0.3% in that study. Den Hartog et al[7] with a mean follow-up of 6 years noted in their study that the risk of stroke in aCAS overall was 0.4% and in cases of severe stenosis 0.5%. A 10-year follow-up study of the ACST-1 trial showed a stroke risk of 10% at 5 years, and 16.9% at 10 years in the arm where immediate revascularization was deferred.[8]

In a more recent study, Chang et al[9] noted the incidence of stroke after a mean follow-up of 4.1 years and found a mean annual stroke rate of 0.9% and 5-year risk of ipsilateral stroke of 4.7%. Gologorsky et al[10] studied the natural history of moderate aCAS (50–69%) with a mean follow-up of 5 years where they observed 1.6% of patients developed ipsilateral ischemic stroke with a crude annual risk of 0.31%. Howard et al tried to determine the relation of stroke risk with the degree of stenosis in aCAS through their prospective population-based study [Oxford Vascular Study – OxVasc], systematic review, and meta-analysis, and found out a linear increase in stroke risk with degree of stenosis.[11]

The different rates of stroke incidence across the studies are due to variable inclusion criteria of degree of stenosis, methods to determine the degree of stenosis, and the

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study period (older study participants were not under optimal/best medical management). The presence of various risk factors, genetic predisposition for atherosclerosis, and medical management practices involving risk factor control are also variable across the studies which could influence the degree of stenosis progression and stroke incidence on follow-up. The presence of competing etiologies can also influence stroke incidence among these patients.

Increased Risk of Cognitive Decline

It has been known for some time that a strong link exists between stroke and cognitive decline,[12] and that carotid steno-occlusive disease is associated with some degree of cognitive decline.[13] Paraskevas et al in their systematic review found that among 94% of studies, at least one cognitive test was impaired in patients with aCAS.[14] Memory impairment and executive dysfunction are the usually described cognitive deficits.[15,16] The expected distribution (for all percentile ranks) was significantly below the values for the general population, and this difference was maximum for higher percentiles ($p < 0.0001$ for 50th, 75th, and 95th percentiles, and $p < 0.015$ for 25th percentile).[15]

Initial studies postulated the occurrence of silent cortical infarctions and white matter hyperintensities as the main cause for this cognitive decline.[16] But the recent literature suggests the reduced cerebral perfusion and impaired cerebrovascular reserve as the principal mechanism contributing to cognitive decline in these patients.[14] But right now evidence supporting carotid revascularization to improve or halt this cognitive decline is lacking.[14]

How Should We Treat Asymptomatic Carotid Stenosis?

There are only a few other topics in vascular neurology with more inconsonant and contentious views, and practice variations concerning the best management of patients as in asymptomatic carotid stenosis. With the proven benefit of reduction in stroke occurrence after carotid revascularization (carotid endarterectomy [CEA] or carotid artery stenting [CAS]) for symptomatic carotid stenosis (CS) in the two landmark trials, namely, North American symptomatic carotid endarterctomy trial (NASCET) and European carotid surgery trial (ECST), clinicians were curious if the benefit could be translated to asymptomatic carotid stenosis as well.[17,18] The landmark trials comparing the efficacy of carotid revascularization versus best medical management in aCAS patients are the Veterans Affairs Cooperative Study (VACS), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST).[19,20,21] The best medical management has significantly evolved over the same time posing the question of which would be better for the patient.

Current Guidelines in the Management of Asymptomatic Carotid Stenosis (ACS) (Table 14.1)

Carotid Revascularization

In the VACS, the cumulative ipsilateral neurological events (Transient Ischemic Attack [TIA], stroke, and transient monocular blindness)

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occurred significantly more in the medically managed group (20.6% vs. 8% in the surgical group; $p < 0.001$). But, for the combined incidence of stroke (including contralateral side), myocardial infarction (MI), and death, there was no statistically significant difference between the groups[19] In the ACAS study, the aggregate risk of stroke or any perioperative event over 5 years was shown to reduce by 53% (11% in the medically treated vs. 5.1% in the surgical group).[20] In contrast to moderate stenosis cases determined angiographically and included in the VACS (>50%) and the ACAS (>60%), the ACST included patients with stenosis >70% measured using ultrasound.[21] Also, some of the patients in the ACST were on statins. Immediate CEA has halved in the next 5-year stroke risk from about 12% to about 6% (including the 3% perioperative risk) and interestingly half of this benefit involved disabling or fatal strokes. Net benefit and gain remained in similar trends at 10 years follow-up in this study including the fact that 50% of the benefit was with reduction of fatal strokes or death.[8]

Best Medical Management

The definition and purview of the best medical management are not completely defined and neither have their effect been completely measured or studied to date. But the broad understanding has changed, allowing the inclusion of counseling on diet, lifestyle changes (e.g., moderate exercise), advanced smoking cessation therapies (newer nicotine replacement strategies), and newer classes of drugs for dyslipidemia (newer and potent statins, PCSK-9 inhibitors), diabetes (DPP-4 inhibitors, SGLT-2 inhibitors, newer insulins, GLP-1 analogs), and hypertension.

The indirect evidence is from the Treating to New Targets (TNT) trial where high-intensity statin therapy given for coronary artery disease has shown up to 25% reduction in stroke.[22] Amarenco et al, in a meta-analysis with 90,000 patients, showed that with every 10% reduction in LDL cholesterol, there is estimated stroke risk reduction of 15.6%.[23] Moreover, medical management alone is three to eight times more cost-effective.[24] In a recent trial, Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE-2), both carotid endarterectomy and stenting were not shown to be superior to best medical management both for stroke or death in 30 days, and ipsilateral stroke at 5 years.[25] This trial done after the widespread use of statins and other best medical management practices did not show superiority of the revascularization for aCAS.

The best medical management used in the three landmark trials includes aspirin and medical risk factor control (through pharmacological and nonpharmacological approaches). The first FDA-approved statin, i.e., lovastatin, was commercially available only from September 1987, by which time most of the recruitment for these trials had occurred, and these drugs were not widely available or used at that point in time. These newer classes of medicines are also postulated to have pleomorphic effects beyond the traditional risk factor control; thus, they have the potential to alter the course of atherosclerotic disease in patients. Earlier randomized controlled trials (RCTs) did not use high-intensity statins, strict targets for blood pressure, blood sugar, and lipid levels (which have evolved in the recent years), and the more sophisticated lifestyle-altering measures.

Is It Time to Give Up Carotid Revascularization in aCAS?

With the advancements in best medical treatment (BMT), the stroke rate has reduced in aCAS to <1%.[24,26] As the risk of stroke in aCAS is less, to achieve an advantage of

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revascularization over BMT in aCAS patients, the risk associated with the revascularization should be significantly low. For this reason, 2011 American Heart Association/American Stroke Association (AHA/ASA) guidelines mentioned "the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3% threshold for complication rates may be high because of interim advances in medical therapy" (**Table 14.1**). It was also suggested that the complications of digital subtraction angiography should be considered as part of the risk of surgery because a cerebral angiogram would not have been performed if surgery was not contemplated. So careful selection of patients was advocated in 2011 AHA/ASA guidelines for choosing aCAS patients for revascularization. However, the criteria for this "highly selected" subgroup were not defined in this guideline. Also, carotid revascularization is not advised for cognitive decline associated with aCAS, as there is no sufficient evidence,[27] and multiple studies documented the risk of cognitive decline due to periprocedural stroke post carotid revascularization even in aCAS.[28]

Abbott et al[29] reviewed common misconceptions of adequacy of medical management alone for aCAS. They say the principal benefit shown in the ACST is between immediate and deferred CEA groups, where actually the BMT alone group was lacking for comparison. They also pointed out that CAS is not an answer for all "high-risk" CEA patients due to the fact that there is increased periprocedural stroke in these patients and neither was the superiority of CAS over BMT proven. Logically and as shown by Howard et al, the degree of stenosis correlates with the risk of stroke even in aCAS patients, but the major RCTs did not show difference in benefit between moderate and severe stenosis groups. So, the notion that mere presence of severe stenosis in aCAS patients warrants revascularization may not hold its ground.

Other rebuttals advocating revascularization are the improved procedural techniques leading to less periprocedural strokes and medical management alone will not prevent all strokes. Definitely we may never have BMT that would prevent all strokes. But these in itself are not sufficient enough arguments to advocate procedure for all the patients, because the procedural and periprocedural risks still do not abate completely. Although randomized data are usually superior and required in formulating our practices, this scenario warrants change in practice to BMT over revascularization because of the reasons above discussed pending future well-formulated RCTs comparing current BMT to CAS or CEA done with latest technological advancements.

Does This Mean There Is No Role for Revascularization in aCAS?

First, to achieve an advantage over noninterventional BMT, CEA or CAS must be performed with the lowest possible risk of stroke. Therefore, the guidelines state, for <3% risk of periprocedural stroke, MI or death is a reasonable standard to consider revascularization in aCAS patients. This may be achieved with current technological advances in the surgical and endovascular techniques and improved practitioner skills. As discussed earlier, if this risk can be reduced to <1% and if made cost-effective, it can again raise the question of BMT versus routine revascularization for all aCAS.

Second is choosing an appropriate case for revascularization. With current BMT, all aCAS cases are not candidates for revascularization as discussed. However, the challenge lies in the identification of this select small subgroup of aCAS patients. Many studies have been done to find the biomarkers, risk scores, and radiological signs for identifying these patients. In 2017, the European Society for Vascular Surgery (ESVS) proposed a clinical

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Table 14.1 Guideline recommendations of various associations on the management of various asymptomatic carotid stenosis

European Stroke Organisation guideline (2021)[30]	• In patients with >60% ACS considered to be at increased risk of stroke on BMT alone, CEA is recommended (Quality of evidence: Moderate +++, Strength of recommendation: Strong for CEA). • In patients with ACS, CAS is not recommended as an alternative to BMT alone (Quality of evidence: Very low +; Strength of recommendation: Weak against CAS).
Society for Vascular Surgery guideline (2021)[31]	• In low surgical risk patients with >70% ACS (documented by validated duplex ultrasound or computed tomography angiography) CEA plus BMT is recommended over BMT alone for the long-term prevention of stroke and death (Grade I; Quality of evidence: B).
German-Austrian guidelines (2020)[32]	• In the presence of a 60 to 99% ACS, CEA should be considered, provided there is no increased surgical risk and more than one clinical or imaging findings are available that are associated with an increased risk of carotid-related stroke in follow-up (Level of evidence: 1). • In the presence of a 60 to 99% ACS, CAS may be considered, provided there is no increased treatment-associated risk and more than one clinical or imaging findings are available that are presumably associated with an increased risk of carotid-related stroke in follow-up (Level of evidence: 2a). • The periprocedural stroke/death rate should be as low as possible for CEA or CAS for ACS. The in-hospital stroke/death rate should be monitored by expert neurologists and should not exceed 2% (Strong recommendation; Level of evidence: 2a).
European Society for Vascular Surgery guideline (2017)[34]	• In "average surgical risk" patients with a 60 to 99% ACS, CEA should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years (Class IIa; Level of evidence: B). • In "average surgical risk" patients with a 60 to 99% ACS in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years (Class IIb; Level of evidence: B).
AHA/ASA guidelines (2014)[33]	• It is reasonable to consider performing CEA in patients with >70% ACS if the risk of perioperative stroke, MI, and death is <3%. However, its effectiveness compared with contemporary BMT alone is not well established (Class IIa; Level of evidence: A). • Prophylactic CAS might be considered in highly selected patients with ACS (>60% by angiography, >70% by validated Doppler ultrasound), but its effectiveness compared with BMT alone in this situation is not well established (Class IIb; Level of evidence: B). • In ACS patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus BMT alone is not well established (Class IIb; Level of evidence: B).

Abbreviations: ACS, asymptomatic carotid stenosis; BMT, best medical treatment; CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction.
Adapted from Paraskevas KI et al.[43]

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practice guideline[34] in which they have identified clinical and imaging biomarkers associated with increased risk of stroke in aCAS patients:

- *Silent infarction on CT of brain:* With the advent of CT scans, as early as in 1985, Ricotta et al found that up to 20% of patients with aCAS had silent infarcts.[35] In 2009, Kakkos et al[36] for the first time have shown that the presence of silent infarcts is associated with a high risk of stroke, and this risk is noted only in moderate to severe stenosis patients, suggesting these can be high-risk groups who would benefit from CEA. But in a more recent study, Pini et al[37] have described that silent brain infarcts are associated with a statistically significantly higher risk of perioperative stroke or death. Overall, the CEA outcomes in this group are comparable to symptomatic carotid stenosis.
- *Stenosis progression with BMT:* Various studies showed progression of carotid stenosis in about 20% of patients, and this occurs maximum in the first 3 years, and by 8 years, there is zero progression in the plaque. Male gender, hypertension, coronary artery disease, age, plaque area, and elevated creatinine were associated with plaque progression. The risk of future stroke is twice in people with progression of stenosis compared to those without progression.[38]
- *Intraplaque hemorrhage on MRI:* Intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap on MRI of carotid plaque are associated with increased risk of future stroke or transient ischemic attack in patients with carotid atherosclerotic disease.[39] Foam cell formation occurs due to inflammation caused by LDL deposition in the plaque; subsequently, apoptosis and necrosis of this foam cells lead to lipid-rich core. Intraplaque hemorrhage could occur due to disruption of fragile plaque neovessels or due to fissures or disruption of the fibrous cap. All these together increase the risk of plaque rupture. Intraplaque hemorrhage is associated with a high risk of all the carotid MRI biomarkers.[40]
- *Spontaneous embolization on transcranial Doppler (TCD):* In the Asymptomatic Carotid Emboli Study (ACES), a prospective observational study, more than double the risk of stroke was noted in patients with spontaneous emboli detected on TCD, even after controlling for the degree of stenosis, antiplatelet therapy, and other risk factors.[41]
- *Plaque lucency on duplex ultrasound:* Gupta et al described that increased echo-lucent plaques compared to echogenic plaques are associated with a statistically significant increased risk of stroke across all grades of stenosis severity.[42] But the same study also concluded that the magnitude of the increased stroke risk is not sufficient on its own to identify patients who would benefit from revascularization. Newer technology in ultrasound like using contrast enhancement to detect plaque neovascularization, improved software to measure plaque area and volume, and computerized methods to provide quantitative information on plaque morphology are being currently studied to better identify high-risk plaques.

Ulcerated plaque, severe stenosis, impaired cerebrovascular reserve, and contralateral stroke or TIA were also associated with increased stroke risk.[34]

Paraskevas et al,[43] in their international, multispeciality expert review and position statement, proposed an algorithm for the management of aCAS patients:

- For any patient with >50% aCAS, initiate BMT (which includes lifestyle changes).

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- For frail patients with several comorbidities and life expectancy <5 years, BMT alone.
- For patients with life expectancy >5 years with one or more than one high-risk markers described earlier, revascularization may be considered.

Conclusion

The best intervention is prevention, and the best prevention is noninvasive.[24] BMT is the ideal therapeutic strategy for all aCAS patients. Patients with high-risk markers can be considered for revascularization by careful selection. Further studies to identify more robust clinical, radiological, or other biomarkers are the need of the hour. Large studies to define and study the effect of the optimal BMT should be undertaken. RCTs comparing current BMT with current technologically advanced revascularization strategies are needed.

References

1. Sylaja PN, Pandian JD, Kaul S, et al. Ischemic stroke profile, risk factors, and outcomes in India: the Indo-US Collaborative Stroke Project. Stroke 2018;49(1):219–222
2. Kaul S, Alladi S, Jabeen SA, et al. Intracranial atherosclerosis is the most common stroke subtype: ten-year data from Hyderabad stroke registry (India). Ann Indian Acad Neurol 2018; 21(3):209–213
3. Bonati LH, Jansen O, de Borst GJ, Brown MM. Management of atherosclerotic extracranial carotid artery stenosis. Lancet Neurol 2022;21(3):273–283
4. Kamtchum-Tatuene J, Nomani AZ, Falcione S, et al. Non-stenotic carotid plaques in embolic stroke of unknown source. Front Neurol 2021;12:719329
5. Kim HW, Regenhardt RW, D'Amato SA, et al. Asymptomatic carotid artery stenosis: a summary of current state of evidence for revascularization and emerging high-risk features. J Neurointerv Surg 2023;15(7):717–722
6. The European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. Lancet 1995;345(8944):209–212
7. den Hartog AG, Achterberg S, Moll FL, et al; SMART Study Group. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. Stroke 2013;44(4):1002–1007
8. Halliday A, Harrison M, Hayter E, et al; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;376(9746):1074–1084
9. Chang RW, Tucker LY, Rothenberg KA, et al. Incidence of ischemic stroke in patients with asymptomatic severe carotid stenosis without surgical intervention. JAMA 2022;327(20): 1974–1982
10. Gologorsky RC, Lancaster E, Tucker LY, et al. Natural history of asymptomatic moderate carotid artery stenosis in a large community-based cohort. Stroke 2022;53(9):2838–2846
11. Howard DPJ, Gaziano L, Rothwell PM; Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. Lancet Neurol 2021;20(3):193–202
12. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol 2003;2(2):89–98
13. Chang XL, Zhou HQ, Lei CY, et al. Association between asymptomatic carotid stenosis and cognitive function: a systematic review. Neurosci Biobehav Rev 2013;37(8):1493–1499
14. Paraskevas KI, Faggioli G, Ancetti S, Naylor AR. Editor's choice—Asymptomatic carotid stenosis and cognitive impairment: a systematic review. Eur J Vasc Endovasc Surg 2021;61(6):888–899
15. Lazar RM, Wadley VG, Myers T, et al. Baseline cognitive impairment in patients with asymptomatic carotid stenosis in the CREST-2 trial. Stroke 2021;52(12):3855–3863
16. Paraskevas KI, Mikhailidis DP, Spinelli F, et al. Asymptomatic carotid stenosis and cognitive impairment. J Cardiovasc Surg (Torino) 2023; 64(2):167–173
17. Ferguson GG, Eliasziw M, Barr HWK, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial: Surgical Results in 1415 Patients. Stroke. 1999 Sep;30(9):1751–8
18. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the

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MRC European Carotid Surgery Trial (ECST). Lancet Lond Engl. 1998 May 9;351(9113):1379–87
19. Hobson RW II, Weiss DG, Fields WS, et al; The Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328(4):221–227
20. Walker MD. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273(18):1421–1428
21. Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363(9420):1491–1502
22. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352(14):1425–1435
23. Amarenco P, Labreuche J, Lavallée P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004;35(12):2902–2909
24. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40(10):e573–e583
25. Reiff T, Eckstein HH, Mansmann U, et al; SPACE-2 Investigators. Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial. Lancet Neurol 2022;21(10):877–888
26. Goldstein LB, Bushnell CD, Adams RJ, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42(2):517–584
27. Ancetti S, Paraskevas KI, Faggioli G, Naylor AR. Editor's choice—Effect of carotid interventions on cognitive function in patients with asymptomatic carotid stenosis: a systematic review. Eur J Vasc Endovasc Surg 2021;62(5):684–694
28. Capoccia L, Sbarigia E, Rizzo A, Mansour W, Speziale F. Silent stroke and cognitive decline in asymptomatic carotid stenosis revascularization. Vascular 2012;20(4):181–187
29. Abbott AL, Brunser AM, Giannoukas A, et al. Misconceptions regarding the adequacy of best medical intervention alone for asymptomatic carotid stenosis. J Vasc Surg 2020;71(1):257–269
30. Bonati LH, Kakkos S, Berkefeld J, De Borst GJ, Bulbulia R, Halliday A, et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J. 2021 Jun;6(2):I–XLVII
31. AbuRahma AF, Avgerinos ED, Chang RW, Darling RC, Duncan AA, Forbes TL, et al. The Society for Vascular Surgery implementation document for management of extracranial cerebrovascular disease. J Vasc Surg. 2022 Jan;75(1):26S-98S
32. Eckstein HH, Kühnl A, Berkefeld J, Lawall H, Storck M, Sander D. Diagnosis, Treatment and Follow-up in Extracranial Carotid Stenosis. Dtsch Ärztebl Int [Internet]. 2020 Nov 20 [cited 2024 Sep 28]; Available from: https://www.aerzteblatt.de/10.3238/arztebl.2020.0801
33. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2014 Dec;45(12):3754–832
34. Naylor AR, Ricco JB, de Borst GJ, et al; Esvs Guidelines Committee; Esvs Guideline Reviewers. Editor's choice—Management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55(1):3–81
35. Ricotta JJ, Ouriel K, Green RM, DeWeese JA. Use of computerized cerebral tomography in selection of patients for elective and urgent carotid endarterectomy. Ann Surg 1985;202(6):783–787
36. Kakkos SK, Sabetai M, Tegos T, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. J Vasc Surg 2009; 49(4):902–909

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37. Pini R, Faggioli G, Indelicato G, et al. Predictors and consequences of silent brain infarction in patients with asymptomatic carotid stenosis. J Stroke Cerebrovasc Dis 2020;29(10):105108
38. Kakkos SK, Nicolaides AN, Charalambous I, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg 2014; 59(4):956–967.e1
39. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke 2013;44(11):3071–3077
40. Nies KPH, Smits LJM, Kassem M, Nederkoorn PJ, van Oostenbrugge RJ, Kooi ME. Emerging role of carotid MRI for personalized ischemic stroke risk prediction in patients with carotid artery stenosis. Front Neurol 2021;12:718438
41. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9(7):663–671
42. Gupta A, Kesavabhotla K, Baradaran H, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke 2015;46(1):91–97
43. Paraskevas KI, Mikhailidis DP, Antignani PL, et al. Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement. J Stroke Cerebrovasc Dis 2022;31(1):106182

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15 High-Grade Spondylolisthesis—To Fuse in situ or Reduce

Savitr Sastri B. V.

Introduction

Spondylolisthesis refers to the slipping of one vertebra over another. The word is derived from Greek *spondylos* meaning vertebrae and *oliothesis* referring to slippage.[1]

This clinical syndrome was first described in 1782 by the Belgian obstetrician Herbiniaux.[1] He reported a bony prominence anterior to the sacrum that created an impediment to vaginal delivery in some of his patients. At this point there was little or no understanding of the underlying pathology. In 1853, a German physician Robert reported on specific defects in the pars interarticularis, and these defects were termed spondylolysis by Killian in 1854.[2,3] Killian also proposed that forces imposed by the body's weight caused subluxation of the lumbosacral facets and subsequent anterior translation of the vertebral body. He was also the first to use the term spondylolisthesis. Anatomic studies by Robert and Lambl, in 1855, revealed that a neural arch defect typically preceded this deformity.[4] It was not till 1881 that Neugebauer detailed the clinical and anatomic manifestations of the deformity and suggested that lysis, elongation, and angulation of the pars interarticularis could lead to spondylolisthesis. Neugebauer later came across 10 specimens in which there was gross displacement of the fifth lumbar vertebra. He named this phenomenon spondyloptosis, from the Greek *ptosis* meaning "falling off or down," to indicate a vertebra that is completely dislocated.[5,6]

Spondylolisthesis is classified and graded in multiple ways. The commonest grading is the one proposed by Meyerding.[7] Meyerding's grading is based on the degree of slippage of the posterior border of the superior body when compared to the distance between the anterior and posterior borders of the lower vertebra. This is measured on a standing, neutral radiograph of the lumbar spine. The grades are defined as Grade 1, 0 to 25%, Grade 2, 25 to 50%, Grade 3, 50 to 75%, and Grade 4, 75 to 100%. An additional Grade 5 was added to denote complete slippage of the vertebra—spondyloptosis (**Fig. 15.1**).

Wiltse's classification divides spondylolisthesis based on the etiology.[8] The first type

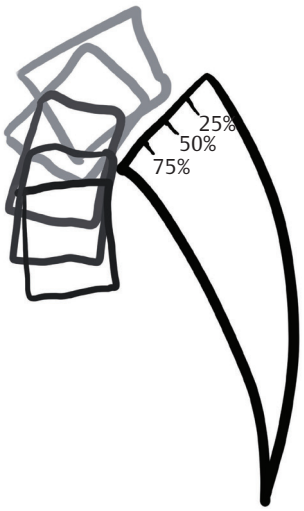

Fig. 15.1 Classification of spondylolisthesis according to Meyerding. The degree of slippage is based on the percentage of the lower body. Grades 1 to 4 being 0–25%, 25–50%, 50–75%, and 75–100%, respectively. Grade 5 is complete slippage—spondyloptosis.

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is congenital dysplasia, including dysplasia of the sacrum or the neural arch of L5. The second type is the isthmic type. This is where the slip is caused due to a defect in the pars interarticularis. There are subtypes of this which include pars lysis, pars elongation, and acute pars fracture. The third type in Wiltse's classification is degenerative listhesis. Types four, five, and six are traumatic, neoplastic, and iatrogenic (**Table 15.1**).

The Marchetti and Bartolozzi classification provides for some prognostic value for slip progression by dividing spondylolisthesis initially into developmental and acquired varieties.[9] It further subclassifies the developmental type into low and high dysplastic types based on the degree of morphological changes in L5 and S1. High dysplasia is characterized by junctional kyphosis, trapezoidal L5 vertebral body, anomaly of the superior end plate of S1, and dysplastic posterior elements of L5 and S1. Low dysplasia includes minimal junctional kyphosis, a rectangular L5 vertebral body, absence of sacral doming, and a nearly normal transverse process. Both were further divided on the basis of the presence or absence of elongation of the pars interarticularis and lysis. The acquired types were traumatic, iatrogenic, pathological, or degenerative. Although this classification does outline high dysplastic slips which will almost always progress, it does not outline objective criteria to define each subtype and does not consider sagittal balance of the spine and spinopelvic balance.

There have been multiple criteria to determine the probability of slip progression, the most important being the grade of slip at presentation, with higher grades tending to progress (>40%). Other criteria include an earlier age of diagnosis, an increased slip angle (**Fig. 15.2**), and presence of significant dysplasia.[10,11]

High-grade lumbar spondylolisthesis is defined as Meyerding's grade 3 and above or a slip percentage of >50%. This is most often seen at L5–S1 and is most often secondary to complete isthmic disruption at L5–S1, since such a degree of anterior translation is not possible with an intact or even elongated pars interarticularis. Rarely high-grade listhesis may also be seen at L4–L5.[12]

High-grade slips will almost always merit surgical intervention. The indications include local and radicular pain, progression of deformity, and cosmetic changes. Untreated high-grade spondylolisthesis can progress and lead to loss of spinopelvic balance, and both deformity and chronic pain.[12]

To date, fusion in situ and reduction and fusion are the two main proposed strategies. Fusion in situ avoids potential neurologic damage but has the risk of pseudoarthrosis, progression of the degree of slip, and persistent cosmetic deformity.[13–15] Reduction is focused on re-establishing sagittal balance and has been shown to have better anterior column support, higher fusion rates, and better cosmetic correction.[16–19] Reduction, especially of high-grade slips, has been associated with a high risk of neurological deficit.

In order to determine the better of the two modes of treatment, it is imperative to

Table 15.1 Wiltse's classification of spondylolisthesis

I: Congenital dysplastic	Incudes dysplasia of sacrum, neural arch of L5
II: Isthmic: defect at pars interarticularis	A: Spondylolytic: stress fracture of pars interarticularis B: Elongation of pars interarticularis C: Acute or traumatic fracture of pars interarticularis
III: Degenerative: long-standing intersegmental instability	
IV: Posttraumatic: defects of posterior elements (aside from pars interarticularis)	
V: Pathologic	

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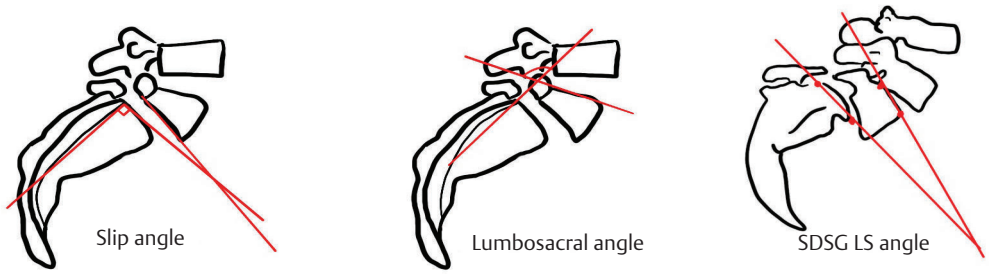

Fig. 15.2 Measurement of slip angle (measured between the perpendicular to the posterior aspect of the S1 vertebra and the lower border of L5), Dubousset's lumbosacral angle (measured between the posterior aspect of the S1 and the upper end plate of the L5), and the Spine Deformity Study Group (SDSG) lumbosacral angle (measured between the upper end plate of S1 and the lower end plate of L5, in high-grade dysplastic listhesis).

understand the pathophysiology of high-grade spondylolisthesis. The evolution of the erect bipedal posture of humans has led to significant alterations in spinopelvic anatomy when compared to even our closest genetic cousins, the apes.[20] The presence of physiologic curves of the spine, the relatively larger pelvic diameter, proximity of the hip joint to the sacroiliac joints, and a more vertical orientation of the sacrum are some of the evolutionary changes that have occurred. This has also led to the lumbosacral junction being substantially strained and prone to significant shear and axial forces. Spondylolysis, or deficiency of the pars interarticularis, is only seen in humans for this reason. The transition of the mobile spine to the far less mobile pelvis via the sacrum leads to two main forces acting across the lumbosacral junction. The gravitational forces that act vertically downward from the head to the pelvis, and the shear forces that act across the L5–S1 disk. Both these give rise to substantial strain on the pars at L5–S1, thus predisposing it to fail.[12]

The next important parameter to consider is the concept of spinal balance. Spinal balance is essential in order that the effort made to maintain an erect posture is the least, or conversely, it is the most energy efficient way to stand and walk. The maintenance of an erect posture is the ultimate goal of the spine and the pelvis. A balanced spine is able to do so with the least amount of energy expenditure.[21,22]

Global sagittal spinal balance is determined by the C7 plumb line. This is a line dropped from the midpoint of the C7 body vertically down. In a balanced spine, the line passes through or behind the middle of the hip joint. Another measure of global sagittal balance is the sagittal vertical axis (SVA). The SVA is measured on full length standing X-rays as the distance from the posterior superior sacral end plate to the C7 plumb line. It is considered positive if it is more than 2 cm in front of the S1 point, and considered negative if it is more than 2 cm behind. Neutral balance is defined as the situation where the C7 plumb line intersects the posterior superior sacral end plate. Mean SVA is between +0.5 and −2.5 cm (**Fig. 15.3**).

Compensatory mechanisms of the lower spine and the pelvis come into play to maintain this balance. Aging, degeneration, or disease processes cause loss of global spinal balance, with the C7 plumb line falling anterior to the hip joint. The first mechanism that is brought in play is increasing the lumbar lordosis. This is done by either increasing segmental lordosis in the lumbar spine or including more segments in the lumbar lordotic segment. When this compensatory change is maximized, the next thing that occurs is progressive retroversion of the pelvis with verticalization of the sacrum.

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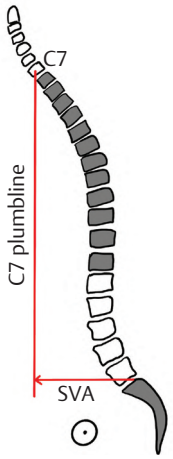

Fig. 15.3 Measurement of global spinal sagittal balance based on the C7 plumb line and the sagittal vertical axis (positive in this example).

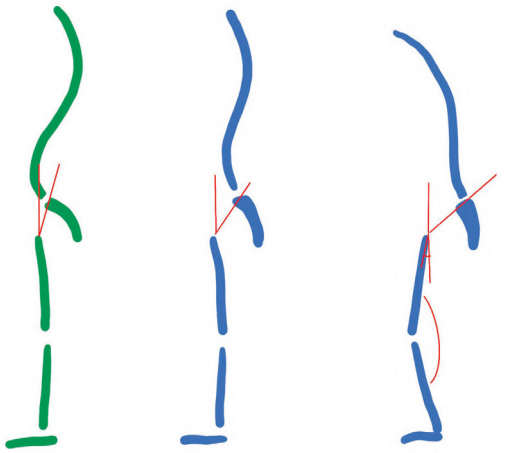

Fig. 15.4 Mechanisms of compensation with progressive loss of sagittal balance. Initial pelvic retroversion with increasing pelvic tilt, and when that is maximized, flexion at the hip and knee. Also shown is measurement of the proximal femoral angle.

The final method that the body uses then to maintain balance is hip flexion and knee flexion (**Fig. 15.4**).

In order to assess and quantify these mechanisms, spinopelvic parameters, sacropelvic parameters, and femoral angles need to be studied and assessed in all patients with high-grade listhesis.

The pelvic parameters have been extensively outlined in multiple publications and a brief outline is presented here (**Fig. 15.5**).

The pelvic incidence or PI is the main pelvic morphometric measurement that determines the relationship between the sacrum and the hip joint. The fundamental idea here being that the sacrum is considered a pelvic vertebra and is the foundation on which the spine stands. Since the sacroiliac joints have little or no movement, the rotation of the pelvis on the hip has long been identified as a significant compensatory mechanism as adult spinal degenerative deformity progresses. It is considered to grow from childhood until reaching its maximal value at adulthood. PI is the angle between two lines: the line perpendicular to the midpoint of the sacral end plate and the line drawn by the union of two points, namely, the midpoint of the sacral end plate and the

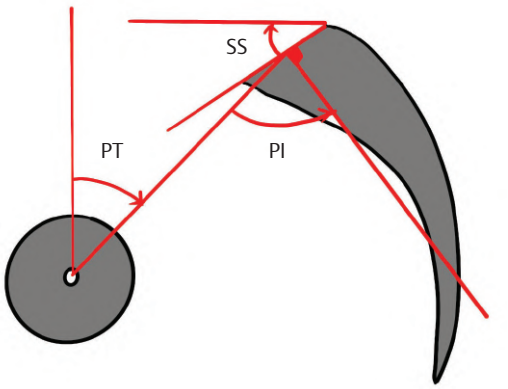

Fig. 15.5 Measurement of standard pelvic parameters of pelvic tilt, sacral slope, and pelvic incidence. The pelvic incidence is the sum of the other two angles.

center of the bifemoral axis (or the midpoint of a line connecting both femoral heads, if they are misaligned). The PI is therefore effectively the sum of the sacral slope (SS), which the angle between the horizontal and the sacral end plate, and the pelvic tilt (PT), which is the angle between the line from the bifemoral

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axis and the midpoint of the sacrum, and the vertical. The PI is believed to be dependent on the morphology of the sacrum and patients with a lower PI have a lower ability to retrovert the pelvis around the hip joint.

This preamble is relevant to understand and utilize the Spine Deformity Study Group (SDSG) classification of spondylolisthesis. This is based on the initial classification by Mac-Thiong and incorporates spinopelvic, sacropelvic, and global sagittal balance parameters in the sorting of spondylolisthesis into seven types (**Table 15.2**).[23–25]

The SDSG classification defines an unbalanced pelvis after Hresko et al, where they found that patients with a higher PI and a lower sacral slope indicate retroversion of the pelvis and sacral verticalization was unbalanced.[26]

In addition, there were low-grade slips (type 3) with high PI, the presence of dysplastic changes that possibly could behave in the manner of higher grades, and thus required further evaluation with spinopelvic parameters including assessment of the sacropelvic balance, as well as lumbosacral kyphosis, proximal femoral angle, and spinopelvic balance, if needed.

The risk factors for progression were outlined earlier, but in addition, in 2009 Lamartina proposed a severity index. This score assessed pelvic retroversion by looking at two measurements. D1 is the distance between the vertical through the femoral heads and the center of the L5 inferior end plate, and D2 is the distance between the center of S2 and the same vertical. The severity index (SI) is D1/D2 expressed as a percentage. In their series they found the SI to be higher than 20% in all high-grade listhesis with propensity to progress. In addition, they also described an unstable zone formed by a square. The gravity line, which is the vertical through the midpoint of the L5 inferior end plate, and the ground reaction line, which is the vertical line through the femoral heads, form the sides and the horizontal from the middle of the S2 body forms the lower side and the upper is extrapolated. Lamartina and colleagues also proposed that all vertebrae within the unstable zone need to be included in the final construct (**Fig. 15.6**).[27]

Treatment Strategies and Rationale

Treatment of patients with high-grade spondylolisthesis hinges primarily on the risk of progression. High-grade slips in asymptomatic adults with few or no symptoms may be managed with observation, physical therapy, and pain control as and when needed. Pediatric or adolescent patients with high-grade slips tend to progress and should be considered for surgery to prevent further worsening of the listhesis.

Table 15.2 Spinal Deformity Study Group classification of spondylolisthesis

Slip severity	Sacropelvic balance	Spinopelvic balance	Type
Low grade	PI <45	-	1
	PI 45–60	-	2
	PI >60	-	3
High grade	Balanced sacropelvis	-	4
	Unbalanced sacropelvis	Balanced spinopelvis	5A
			5B (LSK <80, PFA >10)
	Unbalanced sacropelvis	Unbalanced spinopelvis	6

Abbreviations: LSK, lumbosacral kyphosis; PFA, pelvic femoral angle; PI, pelvic incidence.

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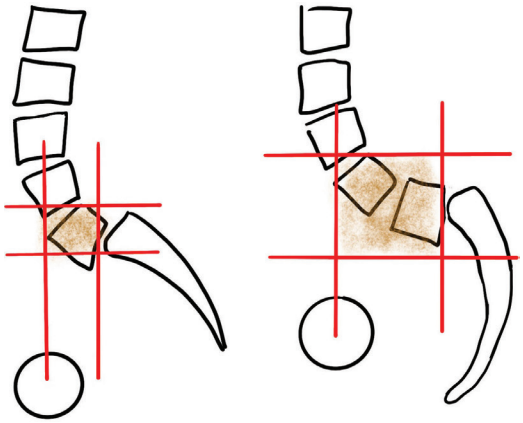

Fig. 15.6 Measurement of severity index. As per Lamartina et al, an index of >20% implies significant pelvic retroversion. By extension, the vertebrae in the instability zone are also calculated (brown) and will need to be instrumented.

Surgical intervention is indicated for management of pain, neurological symptoms, and to halt or reverse progression of the problem, and surgical strategies may be broadly divided into three main types: in-situ fusion, reduction and fusion, and vertebrectomy.

In situ fusion traditionally involved a paramedian Wiltse's approach with placement of bone graft between the transverse process of L5 and the sacral ala. In addition, extension to add L4 with in facet grafts and posterolateral grafts have been described. The advantages of this technique are the ease of surgery and less blood loss. However, the risk of progression of high-grade slips and pseudoarthrosis is present, and in some cases a postoperative cauda equina syndrome has been reported.

Variants of in situ fusion include the Bohlman and Grob methods and the delta fixation described by Abdu et al in 1994 and subsequently by Smith et al in 2001.[28–31] These methods add more robust trans-sacral fixation into L5 with either a fibular strut graft or screws. The delta fixation adds additional fixation points proximally. In situ fusion is often accompanied by wide decompression to prevent neuropraxia and the addition of strut grafts or screws to reduce the incidence of pseudoarthrosis and progression of deformity by adding anterior column support. There are instances however in younger patients with small pedicles where the only option is an uninstrumented posterolateral fusion with a hip spica to maintain the graft till fusion occurs.

Anterior approaches to stabilize high-grade spondylolisthesis include an anterior lumbar interbody fusion (ALIF) for low dysplastic types of listhesis. This is done via a standard retroperitoneal approach with excision of the annulus and disk and placement of a cage, followed by turning the patient prone and adding percutaneous pedicle screw fixation to the construct. In addition to ALIF, a reverse Bohlman technique has also been described, where a standard L4–L5 ALIF is performed, followed by creation of two reamed channels from the anterior surface of L5, going across the disk space and into the sacrum, on either side, which are filled with either a fibular strut graft or a cylindrical cage with graft. The patient is then turned prone, and a posterior decompression and fixation is done.[32]

The reduction techniques are also based on either anterior or posterior approaches. The anterior cantilever technique involves a retroperitoneal approach, and L5–S1 diskectomy followed by careful use of a Cobb's elevator to clear the disk space and perform end plate preparation. A trial implant is then placed and L5–S1 facetectomy is performed. The Cobb's elevator is then placed on the posterior aspect of the sacral dome and used as a cantilever. This maneuver is repeated 3 to 5 times to loosen the ligaments and attain reduction. A large lordotic cage is then placed and anchored to L5 and S1 with small cancellous screws. A posterior fixation is added via Wiltse's approach.[33]

Although these methods do stabilize the olisthetic fragment with fair long-term outcomes, there have been reports of unpredictable outcome and the risk of pseudarthrosis or slip progression can be as high as 50%.[34]

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When posterior in situ fusion is performed, proximal extension of the fusion to L4 vertebra is recommended in order to avoid placing the fusion mass under tension.

Posterior reduction was described by Ruf et al; there have been variations of the same in the literature.[35] The basic principles involved are a wide decompression, osteotomy of the sacral dome if required, and distraction and reduction. This may be done via disk spacers or pedicle screws. Prasad et al have described a technique that involves adding a temporary screw at L2 to provide a longer cantilever arm to antevert the sacrum into place. The reduction must be done with the L5 root under vision and well decompressed to prevent the risk of postoperative neurological deficit.[36]

The last procedure which is often reserved for extreme cases is the Gaines procedure which is a staged vertebrectomy of L5 with direct fusion of L4 over S1.

Mac-Thiong and Labelle have proposed the following workflow for determining the optimal surgical procedure for patients with high-grade listhesis (**Table 15.3**).[23]

First, preoperative posteroanterior (AP) and lateral 36″ radiographs showing the spine, pelvis, and femoral heads are required. An AP Ferguson view of the lumbosacral junction is also done. Radiographs are taken with the knees fully extended and with the upper limbs in the fists-on-clavicle position. The PA radiograph is used to identify any spinal deformity in the coronal plane. The lateral radiograph is used to evaluate the degree of slip, degree of dysplasia, and sagittal spinopelvic balance. A CT scan is obtained preoperatively to evaluate the degree of dysplasia in addition to the degree of spinal and foraminal stenosis. An MRI can be used to identify the nerve roots and cauda equina, and to evaluate for intraspinal abnormalities. In high-grade spondylolisthesis, preoperative MRI is recommended to assess the neuroanatomic relations and the status of adjacent disks. First, the grade of the spondylolisthesis is quantified based on Meyerding's classification. Next the degree of dysplasia is determined based on the presence of the following features:

- Slip angle >10 degrees/Lumbosacral angle of Dubousset <100 degrees/ SDSG lumbosacral angle ≥15 degrees (**Fig. 15.2**).
- Lumbar index <0.8.
- Height of sacral dome >10% length of sacral end plate.
- Presence of L5/S1 facet dysplasia (including spina bifida of L5 and/or S1 involving facets).
- Surface area of both L5 transverse processes <2 cm^2 on the AP Ferguson view.
- L5/S1 disk height <25% of L4/L5 disk height or uniformly dark appearance of L5/S1 disk on MRI.
- Systemic bone or connective tissue disorders.

Next, the spinopelvic balance is ascertained based on Hresko et al[26] for high-grade listhesis—balanced (high SS, low PT) and unbalanced (low SS, high PT). And finally global spinal balance is determined on the long sagittal X-ray, ensuring that the knees are extended. The SDSG classification is based on the fact that of all potential determinants of surgical outcome, the degree of slip

Table 15.3 Surgical algorithm for spondylolisthesis: SDSG classification

Type	Proposed surgery
1	L5–S1 fusion
2	L5–S1 fusion (consider pars repair if indicated)
3	L5–S1 fusion (consider high-grade algorithm if ≥40% slip and dysplastic)
4	In situ instrumented fusion vs. partial reduction with 360-degree fusion
5A	In situ instrumented fusion vs. partial reduction with 360-degree fusion
5B	Partial reduction with 360-degree fusion
6	Partial reduction with 360-degree fusion

Abbreviation: SDSG, Spine Deformity Study Group.

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(low- vs. high-grade), dysplastic changes, and spinopelvic balance are believed to be crucial.[37]

Several meta-analyses of available data comparing in-situ fusion and reduction have been done. In 2017, Jiang et al analyzed three randomized controlled trials (RCTs) and nine observational studies that compared "reduction" and "fusion in situ" for lumbar spondylolisthesis.[37] The findings showed that reduction had advantages in a higher fusion rate and a reduction in slip angle. There were no significant difference between the two processes for clinical satisfaction, complication rate, and blood loss. Patients with in situ fusion reported better clinical satisfaction and a lower complication rate than patients in the reduction group.[38]

In high-grade slips, however, reduction of the spondylolisthesis has many potential advantages when compared to in situ fusion.[37] First, it allows direct decompression of the neural elements by reducing canal and foraminal stenosis. Second, it allows correction of the lumbosacral kyphosis, resulting in improved sagittal spinopelvic balance, gait, biomechanics, and cosmetic appearance. Moreover, reduction can improve the biomechanical environment for fusion by decreasing the tension on the fusion mass. Lastly, it could prevent the risk of acute postoperative cauda equina syndrome. Many surgeons believe that reduction should be given strong consideration in patients with high-grade spondylolisthesis and significant lumbosacral kyphosis.[38]

However, in high-grade patients, the main controversy revolves around the higher complication rate due to the intraoperative distraction of nerve root. Longo et al did not find significant difference between "reduction" and "arthrodesis in situ" for postoperative neurologic deficits; however, pseudoarthrosis was more common in the in-situ group.[31] It is important to note that the lengthening of nerve path resulting from a given amount of translational reduction was significantly greater during the final stages of reduction (50% to fully reduced) than the early stages (100–50%). Therefore, partial reduction is recommended over attempting a complete reduction.

Another meta-analysis by Lak in 2020 showed that in a total of 188 patients analyzed, in situ fusion had a higher mean estimated blood loss (584 mL vs. 451 mL) and a clinically higher incidence of neurologic (48% vs. 15%), pseudarthrosis (13% vs. 8%), and infectious (20% vs. 10%) complications when compared to reduction; however, these differences were not statistically significant. Reduction was associated with a clinically higher incidence of overall complications (32% vs. 25%) and dural tears (22% vs. 7%). Reduction provided better pain relief and greater change in pelvic tilt; however, these differences were not statistically significant.[39]

Koucheki et al analyzed seven studies involving pediatric high-grade spondylolisthesis and compared 97 patients who underwent in situ fixation versus 131 who underwent reduction and fusion with an average follow-up of 8.2 ± 5.1 years. Patients undergoing reduction compared to patients undergoing in situ alone were less likely to develop pseudarthrosis (RR 0.51, 95% CI, [0.26, 0.99], $p = 0.05$). On average, reduction led to 11.97 degrees more reduction in slip angle and 34.8% more reduction in sagittal translation ($p < 0.00001$) compared to in situ fixation. There was no significant difference between patient satisfaction and pain at follow-up. Neurologic complications and reoperation rates were not significantly different.[40]

The ideal surgical strategy for high-grade spondylolisthesis remains a controversial topic with at least overall outcome evidence from limited studies being comparable. There are some studies that show a higher rate of pseudoarthrosis with in situ fusion and others showing a higher rate of neurological complications with reduction. The SDSG classification does provide a guideline that can be followed based on spinopelvic and sacropelvic balance, but more studies will be required to determine the validity of this.

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The current trend of treatment is moving toward reduction and fusion with the idea of restoring spinal balance to prevent progression, pseudoarthrosis, and ensure an optimal outcome.

References

1. Newman PH. Spondylolisthesis, its cause and effect. Ann R Coll Surg Engl. 1955 May;16(5):305-23
2. Fredrickson BE, Baker D, McHolick WJ, et al. The natural history of spondylolysis and spondylolisthesis. J Bone Joint Surg Am. 1984; 66:699–707
3. Wiltse LL. The etiology of spondylolisthesis. J Bone Joint Surg Am. 1962;44-A:539-560
4. Shah S. Spondylolysis and spondylolisthesis. In: Garfin SR, Eismont FJ, Bell GR, Bono CM, Fischgrund JS, eds. Rothman-Simeone and Herkowitz's The Spine. 7th ed. Philadelphia: Elsevier; 2018
5. Ganju A. Isthmic spondylolisthesis. Neurosurg Focus 2002;13(1):E1
6. Newell RL. Spondylolysis. An historical review. Spine 1995;20(17):1950–1956
7. Meyerding HW. Spondylolisthesis. Surg Gynecol Obstet 1932;54:371–377
8. Wiltse LL, Newman PH, Macnab I. Classification of spondylolisis and spondylolisthesis. Clin Orthop Relat Res 1976;(117):23–29
9. Marchetti PG, Bartolozzi P. Classification of spondylolisthesis as a guidance for treatment. In: DeWald RL, Bridwell KH, eds. Textbook of Spinal Surgery. Vol. 2. Philadelphia: Lippincott Wilkins & Williams; 1997:1211–1254
10. Seitsalo S, Osterman K, Hyvärinen H, Tallroth K, Schlenzka D, Poussa M. Progression of spondylolisthesis in children and adolescents. A long-term follow-up of 272 patients. Spine 1991; 16(4):417–421
11. Beutler WJ, Fredrickson BE, Murtland A, Sweeney CA, Grant WD, Baker D. The natural history of spondylolysis and spondylolisthesis: 45-year follow-up evaluation. Spine 2003;28(10): 1027–1035, discussion 1035
12. Mac-Thiong JM, Labelle H. Developmental spondylolisthesis. In: Benzel EC, Steinmetz MP, Berven SH, eds. Benzel's Spine Surgery: Techniques, Complication Avoidance, and Management. Netherlands: Elsevier Health Sciences; 2021
13. Poussa M, Schlenzka D, Seitsalo S, Ylikoski M, Hurri H, Osterman K. Surgical treatment of severe isthmic spondylolisthesis in adolescents. Reduction or fusion in situ. Spine 1993;18(7):894–901
14. Burkus JK, Lonstein JE, Winter RB, Denis F. Long-term evaluation of adolescents treated operatively for spondylolisthesis. A comparison of in situ arthrodesis only with in situ arthrodesis and reduction followed by immobilization in a cast. J Bone Joint Surg Am 1992;74(5):693–704
15. Cheung EV, Herman MJ, Cavalier R, Pizzutillo PD. Spondylolysis and spondylolisthesis in children and adolescents: II. Surgical management. J Am Acad Orthop Surg 2006;14(8):488–498
16. DeWald CJ, Vartabedian JE, Rodts MF, Hammerberg KW. Evaluation and management of high-grade spondylolisthesis in adults. Spine 2005;30(6, Suppl):S49–S59
17. Harris IE, Weinstein SL. Long-term follow-up of patients with grade-III and IV spondylolisthesis. Treatment with and without posterior fusion. J Bone Joint Surg Am 1987;69(7):960–969
18. Lonstein JE. Spondylolisthesis in children. Cause, natural history, and management. Spine 1999; 24(24):2640–2648
19. Sailhan F, Gollogly S, Roussouly P. The radiographic results and neurologic complications of instrumented reduction and fusion of high-grade spondylolisthesis without decompression of the neural elements: a retrospective review of 44 patients. Spine 2006;31(2):161–169, discussion 170
20. Tardieu C, Haeusler M. The acquisition of human verticality. In: Roussouly P, Labelle H, Pinheiro-Franco JL, Gehrchen M, eds. Sagittal Balance of the Spine: From Normal to Pathology: A Key for Treatment Strategy. New York: Thieme; 2019
21. Mardjetko S, Albert T, Andersson G, et al. Spine/SRS spondylolisthesis summary statement. Spine 2005;30(6, Suppl):S3
22. Mac-Thiong JM, Wang Z, de Guise JA, Labelle H. Postural model of sagittal spino-pelvic alignment and its relevance for lumbosacral developmental spondylolisthesis. Spine 2008;33(21):2316–2325
23. Mac-Thiong JM, Labelle H. A proposal for a surgical classification of pediatric lumbosacral spondylolisthesis based on current literature. Eur Spine J 2006;15(10):1425–1435
24. Labelle H, Roussouly P, Berthonnaud E, et al. Spondylolisthesis Classification Based on Spino-Pelvic Alignment. San Antonio TX: Scoliosis

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Research Society 44th Annual Meeting; 2009: 23–26
25. Labelle H, Mac-Thiong JM, Parent S. Pediatric spondylolisthesis. In: Chapman MW, James MA, eds. Chapman's Comprehensive Orthopaedic Surgery. 4th ed. New Delhi, India: Jaypee Brothers Medical Publishers; 2019:4551–4569
26. Hresko MT, Labelle H, Roussouly P, Berthonnaud E. Classification of high-grade spondylolistheses based on pelvic version and spine balance: possible rationale for reduction. Spine 2007;32(20): 2208–2213
27. Lamartina C, Zavatsky JM, Petruzzi M, Specchia N. Novel concepts in the evaluation and treatment of high-dysplastic spondylolisthesis. Eur Spine J 2009;18(Suppl 1):133–142
28. Smith MD, Bohlman HH. Spondylolisthesis treated by a single-stage operation combining decompression with in situ posterolateral and anterior fusion. An analysis of eleven patients who had long-term follow-up. J Bone Joint Surg Am 1990;72(3):415–421
29. Grob D, Humke T, Dvorak J. Direct pediculo-body fixation in cases of spondylolisthesis with advanced intervertebral disc degeneration. Eur Spine J 1996;5(4):281–285
30. Abdu WA, Wilber RG, Emery SE. Pedicular transvertebral screw fixation of the lumbosacral spine in spondylolisthesis. A new technique for stabilization. Spine 1994;19(6):710–715
31. Smith JA, Deviren V, Berven S, Kleinstueck F, Bradford DS. Clinical outcome of trans-sacral interbody fusion after partial reduction for high-grade l5-s1 spondylolisthesis. Spine 2001;26(20): 2227–2234
32. Macagno AE, Hasan S, Jalai CM, et al. "Reverse Bohlman" technique for the treatment of high grade spondylolisthesis in an adult population. J Orthop 2016;13(1):1–9
33. Tu KC, Shih CM, Chen KH, et al. Direct reduction of high-grade lumbosacral spondylolisthesis with anterior cantilever technique—surgical technique note and preliminary results [Internet]. Vol. 22, BMC Musculoskeletal Disorders. Springer Science and Business Media LLC; 2021
34. Longo UG, Loppini M, Romeo G, Maffulli N, Denaro V. Evidence-based surgical management of spondylolisthesis: reduction or arthrodesis in situ. J Bone Joint Surg Am 2014;96(1):53–58
35. Ruf M, Koch H, Melcher RP, Harms J. Anatomic reduction and monosegmental fusion in high-grade developmental spondylolisthesis. Spine 2006;31(3):269–274
36. Sudarshan PK, Suthar HR, Varma VK, Krishnan A, Hegde SK. Long-term experience with reduction technique in high-grade spondylolisthesis in the young. Int J Spine Surg 2018;12(3):399–407
37. Jiang G, Ye C, Luo J, Chen W. Which is the optimum surgical strategy for spondylolisthesis: reduction or fusion in situ? A meta-analysis from 12 comparative studies. Int J Surg 2017;42:128–137
38. Bradford DS, Boachie-Adjei O. Treatment of severe spondylolisthesis by anterior and posterior reduction and stabilization. A long-term follow-up study. J Bone Joint Surg Am 1990;72(7):1060–1066
39. Lak AM, Abunimer AM, Devi S, et al. Reduction versus In Situ Fusion for Adult High-Grade Spondylolisthesis: A Systematic Review and Meta-Analysis [Internet]. Vol. 138, World Neurosurgery. Elsevier BV; 2020:512–520.e2
40. Koucheki R, Rocos B, Gandhi R, Lewis SJ, Lebel DE. Surgical management of high-grade paediatric spondylolisthesis: meta-analysis and systematic review. Eur Spine J 2023;32(2):436–446

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16 Recurrent Lumbar Disk Herniation: Fusion versus Repeat Diskectomy

G. R. Vijay Kumar

Introduction

Lumbar disk herniation is a common clinical problem with an estimated prevalence of 1 to 3% in the general population.[1] A recurrent lumbar disk herniation is defined as the occurrence of a disk prolapse at the same disk level after a relatively symptom-free interval following the primary disk surgery. It may be on the same side as the initial surgery or on the other side.[2,3] Various studies have quoted the rate of recurrent disk prolapses to range between 5 and 18%.[4–6] However, there is still a lack of consensus on the definition of what constitutes a recurrent disk prolapse as opposed to failure of the primary surgery, length of the symptom-free interval from the index prolapse, and whether same side disk prolapse alone should be considered or contralateral prolapses should also be included.[7] The ideal further management of a recurrent disk prolapse when conservative treatment fails also remains debatable, with no clear-cut winner between the two main options of a repeat diskectomy versus a repeat diskectomy with fusion.[8]

Risk Factors for a Recurrent Disk Prolapse

Various studies have tried to identify risk factors for the development of a recurrent disk prolapse following surgery. The patient factors studied which can increase the risk of recurrent prolapse include younger age, male gender, obesity, smoking, trauma, and manual labor.[8–11]

The specific morphology of the annular tear and the type of disk fragment have also been postulated as contributing factors. Carragee et al categorized disk prolapses into four types based on intraoperative appearances and observed on follow-up that the patients with large annular defects and extruded fragments (fragment-defect category) had the highest rate of recurrent disk prolapses.[12]

The degree of aggressiveness during the primary surgery—conservative disk removal/sequestrectomy versus a very thorough curettage to remove as much disk material as possible—has been studied. The result suggested a higher rate of recurrence with conservative diskectomy.[13]

Treatment Options for Recurrent Disk Prolapse

A primary or initial diskectomy for a disk prolapse is indicated when there is a significant neurological deficit like a cauda equina syndrome or a persistent radicular deficit. Persistent radicular pain which is not responding to adequate conservative management for 4 to 6 weeks is also considered an indication for surgical intervention.[14]

However, the indications for surgical intervention in a patient with a recurrent disk prolapse are not as well defined. This is probably because of the technical difficulty of performing redo disk surgery, the higher

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risk of complications like dural tear and nerve root injury, and the somewhat poorer clinical outcomes compared to the primary surgery.[15–17]

But most clinicians would apply the same indications for surgery in a recurrent disk prolapse scenario. Once a decision for surgical intervention has been taken, the surgical options boil down to performing a redo diskectomy (in a variety of different techniques) or performing a redo diskectomy with fusion (again with a variety of different technical options). Addition of a fusion, particularly an instrumented fusion, certainly increases the magnitude, complexity, cost, estimated blood loss, and hospital stay of the redo diskectomy.[18] Thus, it would certainly be worthwhile to analyze the current available literature to determine a logical treatment option for recurrent lumbar disk herniations.

Redo Diskectomy

Repeat diskectomy can be performed as a conventional open diskectomy, as a microdiskectomy, or as an endoscopic diskectomy (either by interlaminar or transforaminal approach). Repeat diskectomy is more technically challenging because of distortion of the local anatomy and scarring around the nerve root. A number of studies have reported a higher rate of complications like dural tear and nerve root injury following a redo diskectomy compared to the index procedure.[16] There are however studies that report no increase in the rate of complications.[19,20] There is also concern with further bone removal during a redo diskectomy and the potential to cause a segmental instability.[21] However, Albayrak et al reported no incidence of iatrogenic instability over a 7-year follow-up period.[19]

Segmental instability itself may be a cause for recurrent lumbar disk herniations. This has been propounded in several publications by Atul Goel.[22,23] Brooks et al performed a systematic review and meta-analysis to identify the potential radiological predictors of recurrent lumbar disk herniations and concluded that segmental instability has a role in recurrence. They felt that early degenerative changes represented by a higher disk height index and latent instability predispose to recurrent disk prolapse. However, with progression of the disk degeneration, there is reduction of the disk height index and reduced segmental motion at the affected segment, thereby resulting in a lesser risk of recurrent herniation.[24]

It would be intuitive to think that a redo diskectomy done through a different access route compared to the primary surgery may be technically less challenging since the anatomical distortion would be lesser and the disk prolapse and nerve root would be accessed through a less scarred corridor. This may explain the relatively lower complication rates reported in a number of studies of endoscopic redo diskectomy.[25,26] Whether a different technique can be utilized for a redo diskectomy would depend on a number of factors like the equipment and infrastructure available, the training background and expertise of the surgeon, and the suitability of the patient for a different approach than for the index surgery.

One of the main concerns with repeat diskectomy is the risk of a further recurrence. There is paucity of data on the long-term rate of further recurrence following a redo diskectomy. The study by Cunha et al reported a rate of recurrence of 30.9% requiring further surgical intervention in their series of 55 patients over a 12-year follow-up period. Most recurrences occurred in the first 2 years after the redo surgery and the risk of needing further surgery decreased after 5 years.[27] Osterman et al in a population-based retrospective study of 35,309 patients in Finland undergoing a diskectomy noted that 14% had a second operation and 2.3% patients had two or more reoperations. They also found that patients having repeat diskectomy had a 25% cumulative risk of having a second reoperation over a 10-year follow-up period.[28] Both the studies noted that the risk of a second recurrence was higher in patients

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who underwent a redo diskectomy within 1 year of the index surgery. Aizawa et al studied the reoperation rate for recurrent lumbar disk prolapse in a Japanese population over a 20-year period and reported a relatively low rate of a same-side, same-level surgery of 0.5% at 1 year, which gradually increased to 2.8% at 15.7 years.[2]

Diskectomy with Fusion

A segmental fusion largely eliminates the risk of any further recurrent disk prolapse at that level. Thus, it makes sense to consider a fusion along with the repeat diskectomy for a recurrent lumbar disk herniation. Mroz et al reported that in a survey of 445 North American spine surgeons on the treatment of recurrent disk prolapse, significant differences existed in the preferred surgical procedure. They also found that surgeons in practice for >15 years were more likely to prefer redo microdiskectomy compared to surgeons with <15 years in practice, who were more in favor of a redo diskectomy with fusion.[29]

Osterman et al found in their population-based study in Finland that the risk of reoperation was considerably lower in patients who underwent a fusion as their first reoperation (5%) compared to a repeat diskectomy (24.9%).[28]

Repeat diskectomy with fusion can be performed using a variety of techniques. Most surgeons would opt to do a posterior instrumented fusion along with the repeat diskectomy. Common techniques of fusion include pedicle screw fixation along with posterior lumbar interbody fusion (PLIF), transforaminal interbody fusion (TLIF), or a posterolateral fusion. The procedure can also be performed through minimally invasive techniques (MIS). Another option that has been exercised is to do an anterior lumbar interbody fusion (ALIF). Phan et al did a systematic review and meta-analysis of the available literature on the results of ALIF surgery for recurrent lumbar disk herniations. They concluded that ALIF and repeat diskectomy is a feasible option in patients with recurrent disk prolapse, with good amelioration of back and leg pain and acceptable level of complications.[30]

Arif et al in a systematic review and meta-analysis of the results of fusion surgery for recurrent disk found that the average success rate was 86.1%, visual analog scale (VAS) leg pain improved by 71%, VAS back pain improved 56%, and rate of complications was 11.4% with 0% rate of recurrence. Their meta-analysis included four studies of fusion by TLIF, one study of MIS-TLIF, and two studies of PLIF.[31]

Most spine surgeons would accept that if fusion is being considered, then some form of interbody fusion is preferable in addition to the pedicle screw fixation. An interbody fusion allows restoration of disk height, improves segmental lordosis, provides anterior column support, and promotes fusion. The two common techniques of performing an interbody fusion are PLIF and TLIF.

Proponents of PLIF have reported high success rates of >90% for the procedure.[32,33] The complication rates are higher for a PLIF procedure in comparison to a TLIF fusion in a number of comparative studies.[31,33] Mehta et al found a higher incidence of nerve root dysfunction and dural tears following PLIF in comparison to TLIF in their series of 119 patients.[34] However, this difference was not found to be statistically significant, probably due to the small numbers. The higher incidence of transient nerve root dysfunction and durotomies could be ascribed to the need for medial retraction of the dural sac during a PLIF procedure. In comparison, since a TLIF procedure uses a far-lateral corridor to access the interbody space, there is minimal thecal retraction or root manipulation.

The results for TLIF showed consistently high success rates across several studies.[35–36] Patients having a TLIF achieved the highest proportion of excellent outcomes (93.3%) in the study by El Shazly et al compared to patients having a PLIF or a redo diskectomy

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alone (86.7%).[35] All these studies confirm the clinical success of TLIF in improving VAS back and leg pain scores, achieving satisfactory fusion, and preventing recurrence of disk herniation at the level. Arif et al reported that the average complication rate of TLIF across several studies in their meta-analysis was 8.4%.[31] The complications reported include dural tear, transient nerve root dysfunction, cerebrospinal fluid leakage, and wound infection.

There is limited literature available on the role of MIS-TLIF in recurrent lumbar disk herniations.[38–40] Erdem et al reported successful outcomes in all patients who underwent a MIS-TLIF for a recurrent lumbar disk herniation in their series of 27 patients.[38] Similarly good results were reported in the study by Liu and Zhou, with excellent/good results reported by 96% of their patients.[39] All these studies also report reduced postoperative pain, less blood loss, better cosmesis, and minimal rates of complications. However, the surgical procedure is technically challenging and has a relatively steep learning curve.

Summation of Evidence and Rationale for Treatment

A recurrent disk prolapse following diskectomy for the index prolapse is a relevant possibility, with a quoted rate of 5 to 18% in the literature. The available evidence for the treatment of a recurrent lumbar disk herniation largely comprises of retrospective case series and comparison studies with limited temporal follow-up.

The initial treatment for a recurrent disk prolapse should follow the same algorithm as for the primary disk prolapse, with conservative care comprising of analgesia and physiotherapy, usually for a period of 4 to 6 weeks. Surgery is indicated in the presence of a cauda equina syndrome or significant and/or worsening radicular neurological deficit. Surgery is also considered for persistent symptoms despite adequate conservative care.

The surgical options broadly fall into two categories—repeat diskectomy alone or repeat diskectomy with fusion. Repeat diskectomy alone has been shown to be effective in relieving the back and leg pain, enabling return to work and normal activities. Advantages include a shorter operation time, lesser hospital stay, lesser blood loss, and lower cost compared to diskectomy with fusion. The surgical complication rates have not shown any significant difference in comparison to fusion. The most frequent complications are dural tears with cerebrospinal fluid leak and nerve root dysfunction. There is some evidence that this risk of complications can be potentially reduced or mitigated by choosing a different surgical approach for the redo diskectomy from the index surgery, thereby avoiding the area of scarring and altered anatomy.

The principal drawback of repeat diskectomy alone is that it potentially leaves the door open for a subsequent recurrence of the disk herniation. There is limited evidence available in the literature to quantify this risk of a second recurrence, which is thought to be about 25% cumulative risk of having a further surgical intervention over a 10-year period. The other potential drawback is the likelihood of creating or worsening segmental instability. This is attributed to excessive bone removal leading to facetal incompetence and/or to denervation of the erector spinae leading to muscle atrophy. Apart from the traditional open diskectomy, various other techniques like microdiskectomy, tubular retractor diskectomy, and endoscopic (both transforaminal and interlaminar) diskectomy techniques have been propagated to potentially mitigate the complications from redo diskectomy. Although individual case series have shown favorable results for one technique over the other, most systematic reviews and meta-analysis of pooled data have

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shown no significant statistical superiority of any of these techniques in terms of patient outcomes or complications.

Fusion along with repeat diskectomy was proposed to minimize the possibility of any further disk herniations at the operation level. It would also stabilize any segmental instability. It was believed that it would also benefit patients who had significant back pain in addition to the radicular pain. Although studies have confirmed reduction in the rate of recurrent disk herniations in the operated segment, the rate of reoperation following fusion has not been shown to be statistically significantly different compared to diskectomy alone because of reoperations for implant-related issues and surgery for adjacent segment disease.

Posterior fusion with diskectomy usually involves transpedicular fixation along with an interbody fusion by PLIF of TLIF. A few studies have also described case series of patients undergoing an ALIF for a recurrent disk herniation. Any practical or theoretical advantages that may be conferred by the addition of fusion to diskectomy has to be weighed against the increase in operating time, hospital stay, blood loss, and cost, which most studies and systematic reviews confirm to be higher for a fusion procedure. Systematic reviews and meta-analysis of pooled data from studies have also not shown any statistically significant difference in clinical outcomes in terms of relief of back or leg pain and return to work between diskectomy alone versus diskectomy and fusion.

Early recurrence of a disk prolapse (within 1 year of the index surgery) has been shown to have a higher possibility of a second recurrence. Large annular defects seen or created at the time of the index surgery are also associated with an increased incidence of recurrent herniation. A recurrent lumbar disk herniation in a patient with these criteria being positive may warrant a redo diskectomy with a fusion.

Conclusion

Recurrent lumbar disk herniations can be treated by diskectomy alone or by diskectomy with fusion. The available evidence does not show clear superiority of one technique over the other across all patient categories in terms of clinical outcome. Diskectomy alone is more commonly performed, particularly with the advent of minimally invasive and endoscopic techniques. Diskectomy with fusion is a more complex procedure with a higher cost.

All patients should be evaluated individually and assessed for the presence of predominant back pain, presence of clinical or radiological instability, nature of work or physical fitness requirement, and risk of a further recurrent herniation and then a choice should be made for diskectomy alone or for diskectomy with fusion.

References

1. Jordan J, Konstantinou K, O'Dowd J. Herniated lumbar disc. Clin Evid 2011;2011:1118
2. Aizawa T, Ozawa H, Kusakabe T, et al. Reoperation for recurrent lumbar disc herniation: a study over a 20-year period in a Japanese population. J Orthop Sci 2012;17(2):107–113
3. Greenleaf RM, Harris MB, Bono CM. The role of fusion for recurrent disk herniations. Semin Spine Surg 2001;23(4):242–248
4. Crock HV. Observations on the management of failed spinal operations. J Bone Joint Surg Br 1976; 58(2):193–199
5. Ebeling U, Kalbarcyk H, Reulen HJ. Microsurgical reoperation following lumbar disc surgery. Timing, surgical findings, and outcome in 92 patients. J Neurosurg 1989;70(3):397–404
6. Law JD, Lehman RA, Kirsch WM. Reoperation after lumbar intervertebral disc surgery. J Neurosurg 1978;48(2):259–263
7. Swartz KR, Trost GR. Recurrent lumbar disc herniation. Neurosurg Focus 2003;15(3):E10
8. Dower A, Chatterji R, Swart A, Winder MJ. Surgical management of recurrent lumbar disc herniation and the role of fusion. J Clin Neurosci 2016; 23:44–50

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9. Drazin D, Ugiliweneza B, Al-Khouja L, et al. Treatment of recurrent disc herniation: a systematic review. Cureus 2016;8(5):e622
10. Simpson JM, Silveri CP, Balderston RA, Simeone FA, An HS. The results of operations on the lumbar spine in patients who have diabetes mellitus. J Bone Joint Surg Am 1993;75(12):1823–1829
11. Suk KS, Lee HM, Moon SH, Kim NH. Recurrent lumbar disc herniation: results of operative management. Spine 2001;26(6):672–676
12. Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: the effects of fragment type and anular competence. J Bone Joint Surg Am 2003;85(1):102–108
13. Watters WC III, McGirt MJ. An evidence-based review of the literature on the consequences of conservative versus aggressive discectomy for the treatment of primary disc herniation with radiculopathy. Spine J 2009;9(3):240–257
14. Spengler DM, Freeman CW. Patient selection for lumbar discectomy. An objective approach. Spine 1979;4(2):129–134
15. Burton CV, Kirkaldy-Willis WH, Yong-Hing K, Heithoff KB. Causes of failure of surgery on the lumbar spine. Clin Orthop Relat Res 1981;(157): 191–199
16. Palma L, Carangelo B, Muzii VF, Mariottini A, Zalaffi A, Capitani S. Microsurgery for recurrent lumbar disk herniation at the same level and side: do patients fare worse? Experience with 95 consecutive cases. Surg Neurol 2008;70(6): 619–621, discussion 621
17. Fager CA, Freidberg SR. Analysis of failures and poor results of lumbar spine surgery. Spine 1980; 5(1):87–94
18. Katz JN. Lumbar spinal fusions: surgical rates, costs, and complications. Spine 1995;20(24 Suppl): 78S–83S
19. Albayrak S, Ozturk S, Durdag E, Ayden Ö. Surgical management of recurrent disc herniations with microdiscectomy and long-term results on life quality: Detailed analysis of 70 cases. J Neurosci Rural Pract 2016;7(1):87–90
20. Hou T, Zhou Q, Dai F, et al. Repeated microendoscopic discectomy for recurrent lumbar disk herniation. Clinics (Sao Paulo) 2015;70(2):120–125
21. Musa G, Barrientos REC, Makirov SK, et al. Repeat discectomy for recurrent same level disc herniation: a literature review of the past 5 years. Surg Neurol Int 2023;14:100
22. Goel A, Patil A, Shah A, et al. Lumbar radiculopathy: outcome analysis following treatment by only fixation—a report of an early experience of 44 cases. J Craniovertebr Junction Spine 2019;10(4):203–209
23. Goel, A. Is disc herniation "secondary" to spinal instability? Is it a protective natural response? Journal of Craniovertebral Junction and Spine 2021;12(3):213-215
24. Brooks M, Dower A, Abdul Jalil MF, Kohan S. Radiological predictors of recurrent lumbar disc herniation: a systematic review and meta-analysis. J Neurosurg Spine 2020;34(3):481–491
25. Shin KH, Chang HG, Rhee NK, Lim KS. Revisional percutaneous full endoscopic disc surgery for recurrent herniation of previous open lumbar discectomy. Asian Spine J 2011;5(1):1–9
26. Hoogland T, van den Brekel-Dijkstra K, Schubert M, Miklitz B. Endoscopic transforaminal discectomy for recurrent lumbar disc herniation: a prospective, cohort evaluation of 262 consecutive cases. Spine 2008;33(9):973–978
27. Cunha M, Basto D, Silva PS, Vaz R, Pereira P. Long-term outcome of redo discectomy for recurrent lumbar disc herniations. Eur Spine J 2023;32(2):534–541
28. Osterman H, Sund R, Seitsalo S, Keskimäki I. Risk of multiple reoperations after lumbar discectomy: a population-based study. Spine 2003; 28(6):621–627
29. Mroz TE, Lubelski D, Williams SK, et al. Differences in the surgical treatment of recurrent lumbar disc herniation among spine surgeons in the United States. Spine J 2014;14(10):2334–2343
30. Phan K, Lackey A, Chang N, et al. Anterior lumbar interbody fusion (ALIF) as an option for recurrent disc herniations: a systematic review and meta-analysis. J Spine Surg 2017;3(4):587–595
31. Arif S, Brady Z, Enchev Y, Peev N. Is fusion the most suitable treatment option for recurrent lumbar disc herniation? A systematic review. Neurol Res 2020;42(12):1034–1042
32. Li L, Liu Y, Zhang P, Lei T, Li J, Shen Y. Comparison of posterior lumbar interbody fusion with transforaminal lumbar interbody fusion for treatment of recurrent lumbar disc herniation: a retrospective study. J Int Med Res 2016;44(6):1424–1429
33. Huang KF, Chen TY. Clinical results of a single central interbody fusion cage and transpedicle screws fixation for recurrent herniated lumbar disc

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and low-grade spondylolisthesis. Chang Gung Med J 2003;26(3):170–177

34. Mehta VA, McGirt MJ, Garcés Ambrossi GL, et al. Trans-foraminal versus posterior lumbar interbody fusion: comparison of surgical morbidity. Neurol Res 2011;33(1):38–42
35. El Shazly AA, El Wardany MA, Morsi AM. Recurrent lumbar disc herniation: a prospective comparative study of three surgical management procedures. Asian J Neurosurg 2013;8(3):139–146
36. Abd El-Kader Hel-B. Transforaminal lumbar interbody fusion for management of recurrent lumbar disc herniation. Asian Spine J 2016;10(1): 52–58
37. Li Z, Tang J, Hou S, et al. Four-year follow-up results of transforaminal lumbar interbody fusion as revision surgery for recurrent lumbar disc herniation after conventional discectomy. J Clin Neurosci 2015;22(2):331–337
38. Erdem MN, Erken HY, Aydogan M. The effectiveness of non-surgical treatments, re-discectomy and minimally invasive transforaminal lumbar interbody fusion in post-discectomy pain syndrome. J Spine Surg 2018;4(2):414–422
39. Liu C, Zhou Y. Percutaneous endoscopic lumbar diskectomy and minimally invasive transforaminal lumbar interbody fusion for recurrent lumbar disk herniation. World Neurosurg 2017;98:14–20
40. Wang A, Yu Z. Comparison of percutaneous endoscopic lumbar discectomy with minimally invasive transforaminal lumbar interbody fusion as a revision surgery for recurrent lumbar disc herniation after percutaneous endoscopic lumbar discectomy. Ther Clin Risk Manag 2020;16:1185–1193

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17 MIS versus Open TLIF—Results and Complications

Rushabh M. Chheda, Ashutosh Kumar, Vandan Raiyani, and Jayesh Sardhara

Introduction

Transforaminal lumbar interbody fusion (TLIF) is a common surgical procedure for addressing various spinal conditions such as degenerative disk disease, spondylolisthesis, and spinal stenosis. The goal of TLIF is to stabilize spinal segments and promote fusion between vertebrae, which alleviates pain and restores function. There are two primary approaches to performing TLIF: minimally invasive spine surgery (MIS) and open surgery. Each approach has its unique methodologies, advantages, and potential complications, all of which significantly impact patient outcomes.

MIS-TLIF utilizes small incisions, specialized instruments, and advanced imaging to access the spine with minimal tissue disruption. The benefits of MIS-TLIF include reduced muscle and tissue damage, shorter hospital stays, faster recovery times, and lower postoperative pain levels.[1] Patients undergoing MIS-TLIF also experience less blood loss and a reduced risk of infection compared to traditional open surgery.

In contrast, open TLIF involves a larger incision and direct visualization of the surgical site. This method allows for a clear and unobstructed view of the spine, which can be advantageous in complex cases. However, open TLIF is associated with increased muscle and tissue damage, longer hospital stays, extended recovery periods, and higher postoperative pain levels.[1,2] Despite these drawbacks, open TLIF remains a valuable option for certain patients, particularly those with severe or complex spinal conditions.

When comparing MIS and open TLIF, several factors are considered, including surgical indications, outcomes, patient satisfaction, and the incidence of complications. Research suggests that both the techniques can achieve similar rates of spinal fusion and long-term pain relief.[2] However, the minimally invasive approach often results in better short-term outcomes, such as quicker recovery and less postoperative pain.

Complications such as nerve damage, infection, and hardware failure can occur with both approaches, although their incidence rates may differ. Understanding the specific indications, risks, and benefits associated with each technique is crucial for surgeons and patients when determining the most appropriate treatment plan.

Indications for MIS-TLIF versus Open TLIF

The choice between MIS and open TLIF largely depends on the patient's specific spinal condition, the complexity of the case, and the desired outcomes. MIS-TLIF is preferred for its minimal tissue disruption, quicker recovery, and suitability for less severe conditions, such as grade 1 or 2 spondylolisthesis. In contrast, open TLIF is favored for more complex or severe cases requiring extensive visualization and correction, including grade 3 to 5 spondylolisthesis, adult degenerative scoliosis with spondylolisthesis, associated severe spinal deformity, long segment fusion, and cases of re-exploration. Surgeon's expertise is a crucial factor in choosing the surgical strategy.[3] Ultimately, the decision should be made collaboratively between the patient and the

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surgeon, considering the unique circumstances and potential benefits of each approach.

Due to the preferred indications for these two modalities, a clear comparison of their outcomes is challenging due to different patient spectrums. To avoid this confounding factor, we evaluated the literature where a comparison of the two techniques was done for a common pathological status, i.e., similar grade of listhesis.

Results of MIS-TLIF and Open TLIF in Low-Grade Listhesis

Both MIS-TLIF and open TLIF effectively treat low-grade listhesis, providing significant pain relief and functional improvement. Patients with low-grade listhesis have easily recognizable anatomical landmarks on intraoperative fluoroscopy, making MIS-TLIF relatively easier and safer with less radiation exposure. MIS-TLIF also offers benefits such as reduced blood loss, shorter hospital stays, and lower infection rates, making it an attractive option for many patients.

Open TLIF, while more invasive, allows for quicker surgical access and may be preferred in certain clinical situations. The need for radiation exposure is minimal, which can be advantageous for female patients of childbearing age. The reported clinical and radiological outcomes are comparable to MIS-TLIF. However, open TLIF is associated with increased postoperative pain, longer hospital stays, and a higher risk of surgical site infections, making it a less preferred option for low-grade spondylolisthesis.

Comparison of Clinical Outcomes

Patient-reported outcomes, such as the visual analog scale for back pain (VAS-BP) and the Oswestry disability index (ODI), are crucial for assessing the clinical efficacy of surgical techniques.[4] In 2018, Lee et al[5] found that MIS-TLIF offered notable short-term benefits in VAS-BP and ODI scores due to reduced intraoperative tissue damage. However, the long-term efficacy comparison between MIS-TLIF and open TLIF remains contentious (**Fig. 17.1**).

Qin et al[2] reported no significant difference in long-term VAS-BP between the two groups but found MIS-TLIF superior in ODI scores at the final follow-up. Wong et al[6] also noted significantly lower VAS-BP and ODI scores for MIS-TLIF patients at over 1 year of follow-up compared to those undergoing open TLIF. Conversely, studies by Wang et al[7] and Tian et al[8] reported no statistically significant differences in long-term VAS and ODI outcomes between the two approaches. Kasis et al,[9] Park and Ha,[10] and Shunwu et al[11] reported significantly better ODI scores in MIS-TLIF group as compared to open TLIF group in their respective series. However, Schizas et al[1] and Peng et al[12] did not find any significant difference in the follow-up ODI scores between the two groups.

Kaloostian and Gokaslan[13] suggested that as patients recovering from open TLIF heal from extensive soft tissue dissection, they might achieve comparable long-term outcomes to those seen earlier in MIS-TLIF patients. Additionally, meta-analyses by Lin et al[14] indicated that MIS-TLIF had only a minor advantage in long-term VAS-BP scores, consistent with the findings reported by Phan et al.[15]

Qin et al's[2] systematic review found that MIS-TLIF and open TLIF had similar preoperative and postoperative pain scores, complication rates, reoperation rates, and fusion rates. Despite longer operative times, the MIS-TLIF approach was associated with lower intraoperative blood loss, shorter hospital stays, and better long-term functional outcomes. Wang et al[7] reported less sacrospinalis muscle injury and reduced postoperative transfusion requirements with the MIS-TLIF technique. Parker et al[16,17] found that patients who underwent MIS-TLIF demonstrated a reduced duration of postoperative opioid analgesic use and

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Fig. 17.1 **(a)** Sagittal MRI image showing anterolisthesis between L4 and L5. **(b, c)** Coronal images showing rotational instability and coronal plane deformity. **(d, e)** X-ray of lumbosacral spine flexion and extension showing grade 2 anterolisthesis of L4 over L5. **(f)** Postoperative X-ray showing fixation of L4–L5 with reduction of anterolisthesis with PEEK cage between L4 and L5.

a faster return to work compared to those who received open TLIF. Additionally, the MIS-TLIF approach was considered a valuable and cost-effective advancement from a societal and healthcare system perspective.

Comparison of Operative Timings

There are conflicting findings regarding operation time. Seng et al[18] reported significantly longer operation times for the MIS-TLIF group, while Singh et al[19] found that MIS-TLIF had shorter surgical times compared to open TLIF. Hong et al[20] reported the mean operative time for MIS-TLIF to be 188.2 ± 42.2 minutes (per one level) and for open TLIF to be 209.6 ± 26.9 minutes, with no significant difference. The increased operative time associated with MIS-TLIF in some studies is likely due to the substantial learning curve required to master this minimally invasive approach. The mean amounts of blood loss during MIS and open TLIF were 246.2 ± 45.8 and 299.1 ± 22.4 mL, respectively, and the mean total amounts of drainage after surgery were 194.1 ± 20.7 and 402.2 ± 33.4 mL, revealing significant differences between the two groups ($P < 0.05$) suggesting added benefits of MIS over open TLIF.[20]

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Comparison of Radiation Exposure

MIS-TLIF relies heavily on intraoperative fluoroscopy or navigation systems to guide the precise placement of instruments and implants through small incisions. This frequent use of imaging results in increased radiation exposure to both the patient and the surgical team. Mroz et al,[21] in a cadaveric study assessing radiation exposure in MIS-TLIF using a biplanar fluoroscope, estimated radiation exposure to the eye at 2.35 mREM/screw and to the ring dosimeter at 10.3 mREM/screw. They reported that radiation exposure to the chest was effectively blocked to a safe level by lead aprons. The extent of radiation exposure is related to the complexity of the radiological anatomy and the surgeon's experience. In our experience, the need for imaging decreases significantly after approximately 10 cases (**Fig. 17.2**).

In contrast, open TLIF requires limited radiation exposure, primarily for determining screw trajectory while marking the entry point based on anatomical landmarks. This significantly reduces radiation exposure to both the surgeon and the patient, offering an advantage over MIS-TLIF.

Comparison of Postoperative Complications

Both Kwon et al[22] and Chan et al[23] reported similar rates of reoperation and degree of fusion between MIS-TLIF and open TLIF. Mueller et al[24] compared the rate of surgical site infection (SSI) between minimally invasive and open surgical procedures for degenerative lumbar pathologies. They reported an overall SSI rate of 1.5%. Although MIS had a significantly lower SSI rate in decompression-only procedures compared to open techniques, there was no difference when decompression and fusion were performed with either technique (0.7% in MIS vs. 2.6% in open).

Results of MIS-TLIF and Open TLIF in High-Grade Listhesis

High-grade spondylolisthesis, typically classified as grade 3 or 4, involves significant slippage of one vertebra over another, often exceeding 50%. Both MIS-TLIF and open TLIF are utilized to address this severe spinal instability (**Table 17.1**). The outcomes and complications associated with each technique in treating high-grade listhesis have been subjects of clinical research and debate.

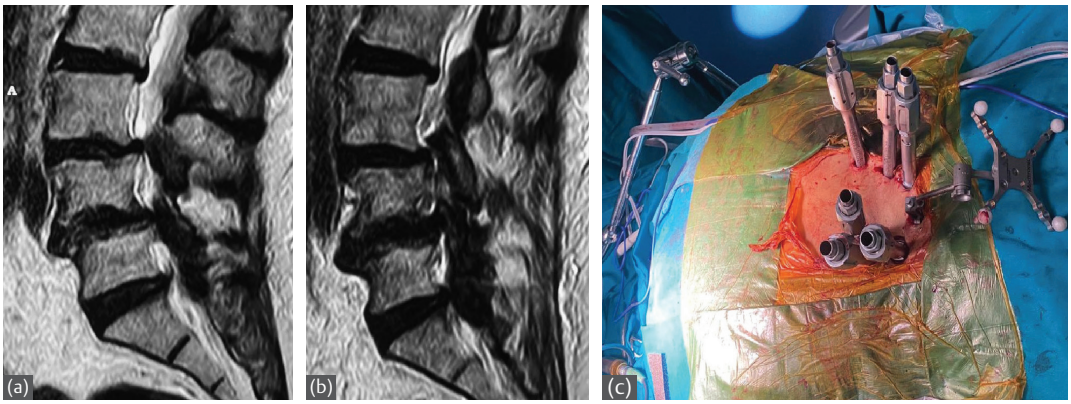

Fig. 17.2 (a–c) Grade 1 anterolisthesis of L4–L5 with disk dessication at L4–L5 with canal compromise with hypertrophic ligamentum flavum. The patient underwent navigation-guided screw placement with minimally invasive spine surgery (MIS) technique. Navigation guidance in anterolisthesis helps in proper placement of screws with postoperative anteroposterior (AP) view showing correct placement of screws.

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Table 17.1 Comprehensive comparision of MIS TLIF with OPEN TLIF based on various parameter

	Studies	Parameter of comparison							
		VAS-BP comparison between group of patients undergoing MIS vs. open TLIF	**ODI comparison between group of patients undergoing MIS vs. open TLIF**	**Minimal clinically important difference (MCID) comparison between group of patients undergoing MIS vs. open TLIF**	**Operative time comparison between group of patients undergoing MIS vs. open TLIF**	**Complications rate comparison between group of patients undergoing MIS vs. open TLIF**	**Blood loss comparison between group of patients undergoing MIS vs. open TLIF**	**Cost comparison between group of patients undergoing MIS vs. open TLIF**	**Length of hospital stay between group of patients undergoing MIS vs. open TLIF**
1.	Mooney et al[31] (*N* = 11,213)	Decrease in back pain at 3 and 12 months was reported as below respectively VAS 3.89 vs. 3.55, p <0.001, 3.96 vs. 3.60, p <0.001 Small, yet consistent decrease in VAS-BP and VAS LP	Lower ODI scores at 3 months (p = 0.036) and 12 months (p = 0.001) postoperatively than those who underwent open lumbar fusion Small, yet consistent decrease in ODI	MCID of 30% in ODI was achieved in a greater proportion of MIS patients than open fusion patients at 3 months (68.2% vs. 65.2% of patients, p = 0.049) and 12 months (74.6% vs. 69.4%, p < 0.001)	Not assessed	MIS was associated with a lower reoperation rate	Not assessed	Not assessed	Not assessed

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	Studies	Parameter of comparison							
		VAS-BP comparison between group of patients undergoing MIS vs. open TLIF	ODI comparison between group of patients undergoing MIS vs. open TLIF	Minimal clinically important difference (MCID) comparison between group of patients undergoing MIS vs. open TLIF	Operative time comparison between group of patients undergoing MIS vs. open TLIF	Complications rate comparison between group of patients undergoing MIS vs. open TLIF	Blood loss comparison between group of patients undergoing MIS vs. open TLIF	Cost comparison between group of patients undergoing MIS vs. open TLIF	Length of hospital stay between group of patients undergoing MIS vs. open TLIF
2.	Wu et al[32] (*N* = 167)	There was reduction in VAS scores post-surgery in both the groups but was not statistically significant at all follow-up time points	There was reduction in ODI scores post-surgery in both the groups but was not statistically significant at all follow-up time points	Not assessed	MIS-TLIF—145.5 ± 21.5 minutes; open TLIF—151.4 ± 19.9 minutes, not statistically significant (*P* = 0.068)	Not assessed	Not assessed	Not assessed	Not assessed
3.	Pokorny et al (meta-analysis)[33] (*N* = 53 studies included)	Not assessed	MIS procedures do not present a significant impact on the reduction of ODI (SMD = −0.14, 95%CI −0.39 to 0.09; *p* = 0.23)	Not assessed	Not assessed	The analysis showed a significant reduction in the risk of complications when adopting an MIS approach (OR = 0.56, 95%CI 0.45–0.69, $p < 0.0001$)	MIS surgeries—significant reduction in surgical blood loss (SMD = −0.79, 95%CI −0.88 to −0.70, $p < 0.0001$)	MIS approaches did exert significant effect regarding costs	Not assessed

(Continued)

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Table 17.1 *(Continued)*

	Studies	Parameter of comparison							
		VAS-BP comparison between group of patients undergoing MIS vs. open TLIF	**ODI comparison between group of patients undergoing MIS vs. open TLIF**	**Minimal clinically important difference (MCID) comparison between group of patients undergoing MIS vs. open TLIF**	**Operative time comparison between group of patients undergoing MIS vs. open TLIF**	**Complications rate comparison between group of patients undergoing MIS vs. open TLIF**	**Blood loss comparison between group of patients undergoing MIS vs. open TLIF**	**Cost comparison between group of patients undergoing MIS vs. open TLIF**	**Length of hospital stay between group of patients undergoing MIS vs. open TLIF**
4.	Qin et al (meta-analysis)[34] (*N* = 394 from a total of 6 studies)	No statistical difference was observed in postoperative VAS-BP score between the two groups (P ¼ 0.32 > 0.05, WMD e0.35)	MIS-TLIF group had a lower postoperative ODI score compared with the TO-TLIF group (P ¼ 0.009 < 0.05)	Not assessed	MIS-TLIF group had a longer operation time compared with the TO-TLIF group (P ¼ 0.0005 < 0.05)	No statistical difference was observed in the complication rate between the two groups (P ¼ 0.70 > 0.05)	Less intraoperative blood loss in the MIS-TLIF group compared with the TO-TLIF group (P ¼ 0.006 <0.05)	Not assessed	The MIS-TLIF group was associated with shorter length of hospitalization compared with the TO-TLIF group (*P* < 0.05)
5.	Subramanian et al[35] (*N* = 62)	Improvements in the VAS for leg pain were similar in both the groups but VAS-BP score reduction was better in MIS group	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	MIS-TLIF group also had a significantly shorter hospital stay and returned to work earlier

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	Studies	Parameter of comparison							
		VAS-BP comparison between group of patients undergoing MIS vs. open TLIF	ODI comparison between group of patients undergoing MIS vs. open TLIF	Minimal clinically important difference (MCID) comparison between group of patients undergoing MIS vs. open TLIF	Operative time comparison between group of patients undergoing MIS vs. open TLIF	Complications rate comparison between group of patients undergoing MIS vs. open TLIF	Blood loss comparison between group of patients undergoing MIS vs. open TLIF	Cost comparison between group of patients undergoing MIS vs. open TLIF	Length of hospital stay between group of patients undergoing MIS vs. open TLIF
6.	Hong et al[20] (N = 97)	The mean postoperative changes in VAS scores were similar between the two groups (P > 0.05)	The mean postoperative changes in ODI scores were similar between the two groups (P > 0.05)	Not assessed	Operative time: MIS-TLIF—188.2 ± 42.2 min (per one level); open TLIF—209.6 ± 26.9 min (P < 0.05)	Not assessed	Mean amounts of blood loss during MIS and open TLIF were 246.2 ± 45.8 and 299.1 ± 22.4 mL	Not assessed	Not assessed
7.	Chan et al[23] (N = 297)	Not assessed	MIS-TLIF was associated with a lower mean ODI at 60 months (18.9 ± 18.4 vs. 24.8 ± 19.0, p = 0.04)	Not assessed	MIS-TLIF was associated with modest increase in operative time (228.2 ± 111.5 vs. 189.6 ± 66.5 minutes, p < 0.001)	Less complications in MIS-TLIF group compared with open TLIF group	MIS-TLIF was associated with less estimated blood loss (108.8 ± 85.6 vs. 299.6 ± 242.2 mL, p < 0.001)	Not assessed	The mean length of hospitalization (MIS-TLIF 2.9 ± 1.8 vs. open TLIF 3.3 ± 1.6, p = 0.08)

Abbreviations: CI, confidence interval; MIS, minimally invasive spine surgery; ODI, Oswestry disability index; open TLIF, open transforaminal lumbar interbody fusion; OR, odds ratio; SMD, Standard Mean Difference; TO-TLIF, Traditional Open TLIF; VAS LP, Visual Analog Scale Leg pain; VAS-BP, visual analog scale for back pain; WMD, Weighted Mean DIfference.

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Open TLIF in High-Grade Spondylolisthesis

For individuals with severe, high-grade spondylolisthesis, there has been a controversy with the treatment approaches. Two different questions to answer here are: first, whether to approach a case of severe grade listhesis with MIS approach or open approach, and second, whether to do an in situ fusion or extensive bony resection and complete reduction. Open surgical techniques might be more suitable. Open approaches allow for more extensive bone removal, reduction maneuvers, and enhanced visualization of neural elements, which can be particularly beneficial in cases with significant anatomical distortion.

Labelle et al[25] found that interbody fusion with partial correction of high-grade spondylolisthesis was sufficient to improve spinopelvic parameters. Conversely, Mac-Thiong and Labelle[26] considered that the reduction of high-grade spondylolisthesis allows direct decompression of the neural elements, corrects lumbosacral kyphosis, reduces tension on the fusion mass, and improves sagittal spinopelvic balance, gait, and aesthetic appearance.

Poussa et al[27] retrospectively reviewed data comparing groups of patients with severe grade listhesis who underwent staged open circumferential reduction and fusion versus in situ fusion. At an average follow-up of 14.8 years, ODI and Scoliosis Research Society (SRS) scores were both significantly improved in the in situ group compared with the reduction group (1.6 vs. 7.2, p ¼ 0.0096, and 90.0 vs. 103.9, p ¼ 0.046, respectively).

The technical complexity of minimally invasive techniques, coupled with the challenging anatomy of high-grade spondylolisthesis, may restrict the feasibility and safety of minimally invasive approaches in these situations.

Expanding the Spectrum of MIS-TLIF to High-Grade Spondylolisthesis

Recent research has shown that MIS approaches can be both feasible and effective for treating high-grade spondylolisthesis. Quraishi and Rampersaud[28] reported positive outcomes using minimal access surgery for mobile high-grade spondylolisthesis. Similarly, Rajakumar et al[29] demonstrated good radiological and patient-reported results with a minimally invasive "rocking" technique for grade 2 and higher lumbar spondylolisthesis.

Furthermore, Patel et al[30] described an MIS-TLIF procedure for patients with high-grade spondylolisthesis and rheumatoid arthritis. This procedure includes disk space preparation, distraction, reduction, and percutaneous screw fixation. They concluded that the MIS-TLIF approach is a viable, safe, and clinically effective option, noting benefits such as reduced blood loss, perioperative pain, and hospital stay, along with reasonable recovery rates, solid fusion, and high patient satisfaction.

Despite the demonstrated feasibility of MIS approaches for high-grade spondylolisthesis, the evidence remains limited. Further research is needed to assess their long-term clinical effectiveness.

Optimizing outcomes in the treatment of lumbar spondylolisthesis requires careful patient selection, surgeon's expertise, and a thorough understanding of the relative advantages and limitations of each surgical approach.

References

1. Schizas C, Tzinieris N, Tsiridis E, Kosmopoulos V. Minimally invasive versus open transforaminal lumbar interbody fusion: evaluating initial experience. Int Orthop 2009;33(6):1683–1688

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2. Qin R, Liu B, Zhou P, et al. Minimally invasive versus traditional open transforaminal lumbar interbody fusion for the treatment of single-level spondylolisthesis grades 1 and 2: a systematic review and meta-analysis. World Neurosurg 2019; 122:180–189
3. Kim CW. Scientific basis of minimally invasive spine surgery: prevention of multifidus muscle injury during posterior lumbar surgery. Spine 2010;35(26, Suppl):S281–S286
4. Rodríguez-Vela J, Lobo-Escolar A, Joven E, Muñoz-Marín J, Herrera A, Velilla J. Clinical outcomes of minimally invasive versus open approach for one-level transforaminal lumbar interbody fusion at the 3- to 4-year follow-up. Eur Spine J 2013;22(12):2857–2863
5. Lee MJ, Mok J, Patel P. Transforaminal lumbar interbody fusion: traditional open versus minimally invasive techniques. J Am Acad Orthop Surg 2018;26(4):124–131
6. Wong AP, Smith ZA, Stadler JA III, et al. Minimally invasive transforaminal lumbar interbody fusion (MI-TLIF): surgical technique, long-term 4-year prospective outcomes, and complications compared with an open TLIF cohort. Neurosurg Clin N Am 2014;25(2):279–304
7. Wang J, Zhou Y, Zhang ZF, Li CQ, Zheng WJ, Liu J. Comparison of one-level minimally invasive and open transforaminal lumbar interbody fusion in degenerative and isthmic spondylolisthesis grades 1 and 2. Eur Spine J 2010;19(10):1780–1784
8. Tian W, Xu YF, Liu B, et al. Computer-assisted minimally invasive transforaminal lumbar interbody fusion may be better than open surgery for treating degenerative lumbar disease. Clin Spine Surg 2017;30(6):237–242
9. Kasis AG, Marshman LAG, Krishna M, Bhatia CK. Significantly improved outcomes with a less invasive posterior lumbar interbody fusion incorporating total facetectomy. Spine 2009; 34(6):572–577
10. Park Y, Ha JW. Comparison of one-level posterior lumbar interbody fusion performed with a minimally invasive approach or a traditional open approach. Spine 2007;32(5):537–543
11. Shunwu F, Xing Z, Fengdong Z, Xiangqian F. Minimally invasive transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases. Spine 2010;35(17):1615–1620
12. Peng CWB, Yue WM, Poh SY, Yeo W, Tan SB. Clinical and radiological outcomes of minimally invasive versus open transforaminal lumbar interbody fusion. Spine 2009;34(13):1385–1389
13. Kaloostian PE, Gokaslan ZL. Evidence-based review of transforaminal lumbar interbody fusion: is minimally invasive better? World Neurosurg 2014;82(1-2):65–67
14. Lin Y, Chen W, Chen A, Li F. Comparison between minimally invasive and open transforaminal lumbar interbody fusion: a meta-analysis of clinical results and safety outcomes. J Neurol Surg A Cent Eur Neurosurg 2016;77(1):2–10
15. Phan K, Rao PJ, Kam AC, Mobbs RJ. Minimally invasive versus open transforaminal lumbar interbody fusion for treatment of degenerative lumbar disease: systematic review and meta-analysis. Eur Spine J 2015;24(5):1017–1030
16. Parker SL, Mendenhall SK, Shau DN, et al. Mini mally invasive versus open transforaminal lumbar interbody fusion for degenerative spondylolis thesis: comparative effectiveness and cost-utility analysis. World Neurosurg. 2014;82:230-238
17. Parker SL, Adogwa O, Bydon A, Cheng J, McGirt MJ. Cost-effectiveness of minimally invasive versus open transforaminal lumbar interbody fusion for degenerative spondylolisthesis associated low-back and leg pain over two years. World Neurosurg 2012;78(1-2):178–184
18. Seng C, Siddiqui MA, Wong KP, et al. Five-year outcomes of minimally invasive versus open transforaminal lumbar interbody fusion: a matched-pair comparison study. Spine 2013; 38(23):2049–2055
19. Singh K, Nandyala SV, Marquez-Lara A, et al. A perioperative cost analysis comparing single-level minimally invasive and open transforaminal lumbar interbody fusion. Spine J 2014;14(8):1694–1701
20. Hong JY, Kim WS, Park J, Kim CH, Jang HD. Comparison of minimally invasive and open TLIF outcomes with more than seven years of follow-up. N Am Spine Soc J 2022;11:100131
21. Mroz TE, Abdullah KG, Steinmetz MP, Klineberg EO, Lieberman IH. Radiation exposure to the surgeon during percutaneous pedicle screw placement. J Spinal Disord Tech 2011;24(4):264–267
22. Kwon JW, Park Y, Lee BH, et al. Ten-year outcomes of minimally invasive versus open transforaminal lumbar interbody fusion in patients with

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single-level lumbar spondylolisthesis. Spine 2022;47(11): 773–780
23. Chan AK, Bydon M, Bisson EF, et al. Minimally invasive versus open transforaminal lumbar interbody fusion for grade I lumbar spondylolisthesis: 5-year follow-up from the prospective multicenter Quality Outcomes Database registry. Neurosurg Focus 2023;54(1):E2
24. Mueller K, Zhao D, Johnson O, Sandhu FA, Voyadzis JM. The difference in surgical site infection rates between open and minimally invasive spine surgery for degenerative lumbar pathology: a retrospective single center experience of 1442 cases. Oper Neurosurg (Hagerstown) 2019;16(6):750–755
25. Labelle H, Roussouly P, Berthonnaud E, Dimnet J, O'Brien M. The importance of spino-pelvic balance in L5-S1 developmental spondylolisthesis: a review of pertinent radiologic measurements. Spine 2005;30(6, Suppl):S27–S34
26. Mac-Thiong J-M, Labelle H. A proposal for a surgical classification of pediatric lumbosacral spondylolisthesis based on current literature. Eur Spine J 2006;15(10):1425–1435
27. Poussa M, Schlenzka D, Seitsalo S, Ylikoski M, Hurri H, Osterman K. Surgical treatment of severe isthmic spondylolisthesis in adolescents. Reduction or fusion in situ. Spine 1993;18(7):894–901
28. Quraishi NA, Rampersaud YR. Minimal access bilateral transforaminal lumbar interbody fusion for high-grade isthmic spondylolisthesis. Eur Spine J 2013;22(8):1707–1713
29. Rajakumar DV, Hari A, Krishna M, Sharma A, Reddy M. Complete anatomic reduction and monosegmental fusion for lumbar spondylolisthesis of Grade II and higher: use of the minimally invasive "rocking" technique. Neurosurg Focus 2017;43(2):E12
30. Patel VH, Peshwattiwar VB. Grade III spondylolisthesis L5–S1 treated by minimally invasive spine transforaminal lumbar interbody fusion (MIS-TLIF) in a patient of rheumatoid arthritis. Indian Spine J 2020;3:91–96
31. Mooney J, Michalopoulos GD, Alvi MA, et al. Minimally invasive versus open lumbar spinal fusion: a matched study investigating patient-reported and surgical outcomes. J Neurosurg Spine 2021;36(5):753–766
32. Wu AM, Hu ZC, Li XB, et al. Comparison of minimally invasive and open transforaminal lumbar interbody fusion in the treatment of single segmental lumbar spondylolisthesis: minimum two-year follow up. Ann Transl Med 2018;6(6):105–105
33. Pokorny G, Amaral R, Marcelino F, et al. Minimally invasive versus open surgery for degenerative lumbar pathologies: a systematic review and meta-analysis. Eur Spine J 2022;31(10):2502–2526
34. Qin R, Wu T, Liu H, Zhou B, Zhou P, Zhang X. Minimally invasive versus traditional open transforaminal lumbar interbody fusion for the treatment of low-grade degenerative spondylolisthesis: a retrospective study. Sci Rep 2020;10(1):21851
35. Subramanian N, Srikantha U, Sitabkhan M, et al. Minimally invasive vs open transforaminal lumbar interbody fusion: early outcome observations. J Spinal Surg. 2015;2(1):1–7

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18 Long-Segment versus Short-Segment Fixation in Thoracolumbar Trauma: When to Do It?

Deepak Bhangale, Sudhir Dubey, and Amrita Endow

Introduction

As the horizons of neurosurgery expand with time, our understanding of age-old spinal fractures undergoes a vast change. This inevitably forces us to re-evaluate our traditional surgical techniques.

The thoracolumbar spine provides the exceptional dilemma of being a junctional zone with high biomechanical stress due to the inherent mobility of the lumbar spine below and the semi-rigidity of the thoracic spine above.

Historically, thoracolumbar fractures were managed with a long-segment fixation, two levels above and below the affected level.[1] The primary aim is stability of the spine and prevention of implant failure.

Among the main advantages of long-segment fixation are strong fixation which allows early mobilization, lower rates of implant failure[2] and less late neurological deficit, and extensive decompression being possible due to the strength of the fixation.[3]

As our understanding of the biomechanics of the spine improved, the focus shifted to preservation of movement and minimizing disruption of supporting soft tissue.

This sparked off a debate: What is the least number of segments one can fix without compromising stability? This in turn gave rise to many questions: Which are the fractures that are at high risk of instability and which allow shorter fixations? Which techniques increase stability in short-segment fixations? Is morphology enough to decide or does load sharing play a more important role? Can we achieve the same degree of decompression and stability via minimally invasive approaches?

And lastly but very importantly, patient factors also play a major role in the decision-making.

History

One of the initial challenges faced in thoracolumbar fixation was the lack of a reliable and reproducible classification system to gauge the instability of the fractures to facilitate surgical decision-making.[4]

Holdsworth in 1970[5] and Denis in 1983[6] succeeded in explaining and classifying the basic characteristics of the fracture, namely, comminution and migration of fragments. Needless to say, although it described the area involved, it failed to adequately describe and classify instability and neurological deficit.

McCormack et al[7] attempted a radically different approach—to integrate implant systems using pedicle screws within their load sharing classification. They considered fracture morphology and instability in terms of comminution, apposition, and kyphosis along with implant failure rates, giving a scoring

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system to predict the likelihood of failure in posterior fixation alone. They recommended subsequent anterior fixation in fractures with scores more than 6. Although it did not account for ligamentous integrity, neurological deficit, longer levels of fixation, and newer implants, it still remains useful for predicting failure of short-segment fixation.

Magerl et al[8] then classified fractures morphologically into compression, distraction, and translation and then further divided them to give the injury type. However, this was difficult to apply in everyday clinical practice.

Following this, the Thoracolumbar Injury Classification and Severity Score (TLICS)[9] in 2005 added the necessary simplification to this classification to allow easy application in clinical practice. This included consideration of neurological deficit and gained immense popularity. However, this classification too had its own share of shortcomings such as the inability to establish treatment protocols for burst fractures without neurological deficits.

Finally, the AOSpine Thoracolumbar Classification[3,10] was introduced which sought to retain the morphological comprehensive description of Magerl et al's classification with the ease of use of TLICS. It also classifies according to neurological deficit and clinical modifiers.

This classification allows us to determine which type of fracture requires surgical intervention and of which type.

Some Definitions

What is long-segment fixation (LSF)?

Fixation of at least two levels above and below the fractured vertebra.

What is mono-segment fixation (MSF)?

Fixation of the fractured vertebra to the superior vertebra, including the intervening level.

What is short-segment fixation (SSF)?

Bisegmental fixation by fixing one level above and below the fractured vertebra.

What Is the Current Belief in Decision-Making?

With the advent of the AOSpine classification,[11] it is possible to treat types A and B with SSF, while type C should be treated with an LSF.

Within types A and B, A3, B1, and B2 may be treated with an MSF as well as SSF.[3]

After the decision for SSF is made, further decision has to be taken on whether anterior supplementation is necessary. As the main pitfall of SSF is implant failure, many have relied on the load sharing classification for this decision.[7,12]

Criticism of the aforementioned classification includes the consideration of first-generation variable screw placement with parallel screw techniques, in addition to not taking ligamentous injury into account.[13] This in turn emphasizes the role of improving implants and surgical techniques in minimizing implant failure, and thereby, making SSF safer.

What Are the Advantages of a Short-Segment Fixation?

The main argument for SSF lies in the preserved mobility for more number of segments, thereby minimizing adjacent-level disease and offering a better quality of life.

A retrospective study[14] reviewed 83 patients with thoracolumbar fractures treated with SSF and showed only 1 patient had to be re-operated for pseudoarthrosis. The study also concluded that there is a drop in the quality of life following this surgery compared to the general population and those undergoing surgical correction for a degenerative etiology. However, that is expected following any major spine surgery and there was no comparison to those with the same pathology managed conservatively or with LSF.

Further, a meta-analysis[15] of nine studies comparing surgically managed thoracolumbar

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burst fractures via SSF and LSF found no significant difference in either in terms of relief of back pain, return to work, and correction of kyphotic deformity.

Another study[16] concluded that patients undergoing SSF have better sexual function and quality of life with their partners as compared to those undergoing LSF.

In addition to preserved mobility, there's the advantage of lower implant cost. Studies have shown that those treated with SSF have less blood loss, less operative time, shorter hospital stay, and less postoperative pain.[2,17] In view of significant advantages of SSF, many advances have been made to improve its safety.

What Are the Surgical Techniques That Make SSF Safer?

Patient Positioning

Positions which stretch the anterior longitudinal ligament and assume a lordotic posture should be preferred as they allow for some degree of reduction. This in turn reduces the risk of implant failure. A four-post frame is preferred over shoulder rolls to achieve the same.[3] Care should be taken in B3 type fractures, for whom this guideline does not apply and may be even dangerous.

Implants and Screw Placement Technique

The traditional polyaxial pedicle screws in a trajectory that is parallel to the end plates puts the majority of the load on the pedicle and creates a right angle at the rod–screw junction.

A study[18] on early failure of short-segment pedicle instrumentation in 52 patients, with trajectories parallel to the end plate, reasoned that their high failure rate was due to untreated anterior instability and pre-stressing of the screws when the rods were contoured in situ. They postulated that any construct not supporting the anterior column of the spine would lead to a powerful bending movement acting on the screw at the point at which it enters the lamina. Furthermore, pre-stressing the screws with forced compression, distraction, or in situ bending leads to more weakening. Also, there is an increase in the chances of implant failure if the reduction is not adequate. In addition to this, polyaxial screws' inherent tendency to submit to the rod's contour further reduces the degree of correction by cantilever mechanisms as some loss of correction by movement of the screw–head interface can be anticipated.[19]

When McCormack et al developed their load sharing classification, they had taken into account this method of vertebral instrumentation. The advent of divergent screw placement however significantly reduced the rates of implant slippage and failure. The divergent screws reduce the compressive load on the anterior column by creating a divergent bridging construct, in contrast to parallel tension band constructs. It also reduces the load at the rod–screw junction.

According to Ouellet et al,[20] the best screw trajectory is "planned as a line from the anterosuperior/anteroinferior corner of the vertebral body running 5 mm above/below the pedicle cortex, allowing for at least a 6-mm screw." The aim is to engage as much cortical bone as possible.

The angle made at the screw–rod junction due to this makes it difficult to fix the rods onto the screws. AOSpine recommends the use of independent connector devices or internal fixation systems for the same. They also recommend a two-step correction—application of lordosis to correct the resultant kyphosis followed by distraction and ligamentotaxis. In situ rod benders and distractors are very useful for the same.[3]

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Load Sharing at the Fractured Level

Many studies[21–25] have shown that index level pedicle screws (at the level of the fracture) substantially decrease the failure rate of implants in SSFs, thereby increasing the effectiveness. In fact, WFNS spine committee recommends that if the fracture level screw cannot be incorporated, LSF should be applied in thoracolumbar burst fractures.[26] One cadaveric study[27] claims that index pedicle screw or supplementation with anterior structural support increases stability by 31%. Another study[28] showed that hyperlordotic reduction and short-segment pedicle screw instrumentation with an intermediate screw had a very low rate of failure regardless of whether the fractures have a high or low load sharing classification score.

A recent systematic review[29] of eight biomechanics studies came to the conclusion that SSF with index screws improves construction stiffness and is comparable to LSF or circumferential reconstruction in thoracolumbar fractures. Another study[30] concluded that SSF with index level screw is comparable to LSF in terms of adequate correction of local kyphotic angle and anterior vertebral height loss while preserving more motion segments.

This is particularly useful to keep in mind in cases with a high degree of comminution where complete reduction is not possible or challenging.

One of the challenges of this method is that instrumentation of bilateral pedicles at the affected level may preclude subsequent anterior decompression. AOSpine thus recommends the use of a single, right-sided pedicle screw, citing similar outcomes.[3]

A study[31] supporting bilateral fixation followed 161 patients undergoing SSF including the fracture level and concluded that it is an effective surgery for patients with single-level thoracolumbar fracture. They further compared outcomes of unilateral and bilateral fixation and found bilateral pedicle screw fixation is more effective than unilateral fixation in maintaining the vertebral height and the stability of the spinal column for AO type A3/A4 fracture in terms of long-term follow-up. They also noted that in patients with anterior vertebral height compressive ratio >50%, the correction loss of the vertebral height, local kyphotic Cobb angle, and vertebral wedge angle at the final follow-up was more obvious, which can be reduced by transpedicular bone grafting.

Ligamentotaxis

SSFs are dependent on tensioning maneuvers to reduce the fractured fragments by making the attached ligaments and periosteum taut. This restores the lost height at the affected level, allowing the fragments to fall back into their place, thus decompressing the canal.

It stands to reason that cases with loss of integrity of the ligaments, especially the posterior longitudinal ligament (PLL), are not amenable to this method. This includes type C, some type B, and A4 fractures. However, some studies claim that even type A4 fractures with a disrupted PLL can be treated with SSF if the decompression and reduction are adequate.[3]

This maneuver is associated with better correction of vertebral height and kyphotic deformity. One study[32] showed better postoperative pain relief as compared to LSF and similar reduction in wedge angle and back pain with SSF (with ligamentotaxis) and LSF. However, in the long term, retaining the reduction in wedge angle was slightly better in the LSF group. A similar finding of better retention of correction in LSF but better early postoperative pain reduction, minimal blood loss, and clinical outcome in SSF was noted by Youssef et al.[17] It is postulated to be due to the mechanical advantage of the longer construct which can be overcome by anterior augmentation or index screws. However, the above studies also demonstrate superior clinical outcomes with SSF which is greatly reliant on ligamentotaxis and adequate reduction.

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Augmentation of Posterior Short Segment Construct

These include the use of cross-links or additional supplemental hook fixation at the levels of the screws. They can be used as an adjunct to posterior pedicle instrumentation.[3,18,25] The addition of cross-links, particularly in SSF, has been biomechanically proven to increase the strength of the construct[26] as well as stiffness,[33] and reduce axial rotation.[33] The XL cross-link provided the highest stiffness (14.9% stiffer than those without a cross-link).[34]

Augmentation with Kyphoplasty

Recent advocacy of kyphoplasty, with or without stent placement, to augment vertebral height gain has gained popularity.[35] One study of 43 patients undergoing posterior SSF including the fracture level combined with kyphoplasty concluded that it is a reliable and safe procedure with satisfactory clinical and radiological results for the treatment of unstable thoracolumbar osteoporotic burst fractures.[36] There is a need to have stronger evidence to support this technique. We have found this technique to be useful, especially in the setting of underlying osteoporosis or pathological bone. Care has to be taken to prevent extravasation of the bone cement.

Combined Anterior and Posterior Approach

In addition to posterior decompression and fixation, a complementary second stage anterior approach is sometimes performed. Using an anterior transthoracic or transabdominal approach, the surgeon can directly visualize the fracture fragment and remove it completely without any traction on the spinal cord or risk of dural injury. If the defect is significant, it can be bridged with an artificial cage or bone graft to restore the height of the anterior column. These techniques are as effective as posterior approaches in neurologically intact patients and even better in terms of restoring vertebral body height and maintaining sagittal balance with comparable outcomes.[37]

A meta-analysis compared anterior and posterior surgeries and found no significant differences between the two. However, the anterior approach was associated with more blood loss.[38]

Anterior fixation allows a reduction in the number of levels fused but carries the risks involved in a second major surgery with a significant chance of blood loss which can be mitigated to some extent by anterior endoscopic decompression and cage placement. This procedure is technically challenging with a steep learning curve, but has fewer major complications compared to the open anterior approach.[39] Anterior approach may be considered in the following cases:

- Incomplete decompression with neuronal deficit, especially with a fragment impacted in the canal.
- Incomplete reduction and restoration of adequate height. This is more commonly seen in case of parallel pedicle screws.
- In select A2 fractures where there is a high rate of pseudoarthrosis and residual kyphosis.

When to Do a Mono-Segment Fixation?

MSF refers to fixing only the injured level by fixing the fractured vertebra to the superior level. It is typically reserved for fractures without severe anterior comminution like types A3, B1, and B2. A clinical trial comparing A3 fractures treated by MSF versus SSF showed similar results in terms of postsurgical pain (visual analog scale [VAS]) and the vertebral kyphotic angle.[40]

One randomized study showed that both monosegment pedicle instrumentation (MSPI) and SSF are effective and reliable operative techniques for select thoracolumbar burst

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fractures. MSPI shortened the operative time and decreased the amount of blood loss significantly, and thus offered better clinical results.[41] Another biomechanical study with finite element models found no significant difference between MSF and SSF in the motion of any functional unit.[42]

MSF also has the obvious advantage of maximum sparing of mobile segments and should be considered a valid alternative to SSF when applicable.

What Are the Advantages of a Long-Segment Fixation?

Posterior approach and fixation of at least two levels above and below the level of fracture is the traditional approach and has the distinct advantage of providing the best stability, including translational and rotational stability.[34,43,44] Especially in cases where neurological deficit is present, the superior stability of the construct allows for wide decompression of the cord.[3] In addition to multiple levels of load sharing, there is an added benefit offered by application of cross-link connectors in open LSFs which is precluded in minimally invasive LSF with percutaneous screws. It has been accepted that in a fracture model, the stability afforded by SSF with index-level pedicle screw remains less than that provided by LSF with or without index screw.[45] Hence, although for most fractures, SSF with an index screw gives acceptable stability, the highly unstable fractures still require an LSF.

When to Do a Long-Segment Fixation?

As mentioned above, in the case of highly unstable fractures, especially type C, with neurological deficit, disruption of both bony columns, and presence of ligamentous injury (not allowing for ligamentotaxis), LSF is needed.[3] In the background of incomplete neurological deficit and severe injuries with shear rotation and flexion extension injuries, LSF is the preferred option. It should also be preferred in cases of ankylosing spondylitis with hyperextension. Additionally, in cases of rotational instability, cross-link connectors should be applied.

What Are the Modifications Which Can Make LSF Better?

All the techniques described in SSF may be applied to LSF to enhance decompression and stability. Also, the number of levels may be adjusted on a patient-to-patient basis.

The primary criticism of LSF is the reduction of mobile levels. Studies have shown that LSFs are known to cause increased movement in adjacent disk spaces leading to raised intradiskal pressure. These biomechanical effects are known to hasten the disk degeneration process.[26,46]

There is evidence to suggest that the load sharing classification does not apply to patients who underwent arthrodesis at more than one level above and one level below the fracture.[47] Hence, it is useful to consider procedures which may reduce even one level while allowing us to avoid a second anterior surgery.

A meta-analysis of 23 publications comparing different posterior spine fixation methods in burst fractures concluded that a fixation method consisting of two levels above and one level below with intermediate index screws for thoracolumbar burst fractures showed the highest correction of kyphosis angle both at immediate and final follow-up and the lowest rate of implant failure at the final follow-up.[48]

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Is Minimally Invasive Better Than Open Surgery in Thoracolumbar Fixation?

Minimally invasive surgery has many advantages: small incisions, minimal dissection of supporting soft tissue, significantly reduced operative time and blood loss, much lower rates of infection, decreased postoperative pain, and short-term disability. The advent of O-arm and navigation guidance have further reduced the complications. On the downside, it has much higher rates of radiation exposure to the surgeon, a longer learning curve, and higher rates of revision.[49]

Because of all the advantages offered, minimally invasive surgery has found its way into the treatment of thoracolumbar fractures as well.

A systematic review of eight articles comparing minimally invasive spine surgery (MISS) and open surgery in severe (types B and C) vertebral fractures showed that there was less operative time, blood loss, and postoperative pain in the MISS group. None of the articles reported major implant failure or long-term neurological deficit in the MISS group. Other outcomes such as functional status (assessed mostly by Oswestry disability index, neurological improvement) and the rate of severe complications remained similar in both the groups.[50]

Another retrospective analysis noted that minimally invasive SSF had the same advantages as mentioned above but resulted in an inferior correction of the wedge angle as well as the vertebral height ratio in the long term. They postulated that it was due to the Schanz screws not being strong enough and the fracture clamp being loosened over time due to soft tissue interposition. They also noted that MISS prevents cross-link application. Additionally, although open SSF fared better radiologically, there was no difference between open SSF and minimally invasive SSF in terms of immediate and long-term postoperative pain, length of stay, and postoperative length of stay. No incidents of implant failure, surgery-related neurological injury, or adjacent segment degeneration were seen in either groups.[32] Another study showed that minimally invasive posterior stabilization using the Sextant system resulted in reduced injury compared with the open surgery during both the internal fixation surgery and the implant removal surgery. They also noted that percutaneous screw fixation through the pedicle of the fractured vertebra showed superior outcomes.[51] To summarize the WFNS spine committee recommendations,[26] minimally invasive techniques may be considered in the treatment of thoracolumbar burst fractures as the evidence suggests equivalent clinical outcomes compared to the open technique.

What Patient Factors Can Influence Our Decision-Making?

The AOSpine classification has included a provision to consider patient-specific modifiers in our decision-making. The neurological status examination differentiates between incomplete and complete injury, marking incomplete injury as "urgent."[10]

LSF is also typically indicated for patients with complete cord injury, elderly patients with pre-existing degenerative disease who are not likely to get benefit from sparing intervertebral motion, and patients with poor compliance to wearing postoperative spinal brace.[52]

Obesity and osteoporosis with poorer bone strength and increased load have shown poorer kyphosis correction and maintenance of vertebral height, with increased implant failures in SSF.[53,54] However, another study suggests similar outcomes in LSF and SSF when SSF is augmented by kyphoplasty.[55]

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It is well known that poorer healing and outcomes are associated with smoking[56] and comorbidities such as diabetes,[57] ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, rheumatological conditions, burns, etc.[3]

Factors affecting stability such as preexisting kyphosis/scoliosis or affecting patient's compliance to postoperative immobilization, wound care, or physiotherapy, such as socioeconomic and educational status, should also be kept in mind during decision-making.

Summary

- Thorough and meticulous classification of injury to determine the type of fracture and instability is essential.
- Unless it is a highly unstable fracture (such as type C) with posterior ligamentous injury or there are other patient factors indicating LSF, SSF should be preferred in view of preservation of motion segments.
- SSF should be augmented with index screws at the fracture level wherever possible to increase stability. In cases of burst fractures, consider LSF if unable to place an index screw with SSF.
- Screws placed in SSF should be divergent and adequate ligamentotaxis should be performed.
- Minimally invasive techniques have shown similar outcomes as open techniques and can be used.
- Anterior fixation can be considered in cases of incomplete decompression or reduction, or in type A2 fractures with pseudoarthrosis.

References

1. Sodhi HBS, Savardekar AR, Chauhan RB, Patra DP, Singla N, Salunke P. Factors predicting long-term outcome after short-segment posterior fixation for traumatic thoracolumbar fractures. Surg Neurol Int 2017;8:233
2. TezerenG,KuruI.Posteriorfixationofthoracolumbar burst fracture: short-segment pedicle fixation versus long-segment instrumentation. J Spinal Disord Tech 2005;18(6):485–488
3. AOSpine Masters Series. Volume 6: Thoracolumbar Spine Trauma [Internet]. Accessed September 11, 2024 at: https://www.thieme.in/aospine-masters-series-volume-6-thoracolumbar-spine-trauma
4. Azam MQ, Sadat-Ali M. The concept of evolution of thoracolumbar fracture classifications helps in surgical decisions. Asian Spine J 2015;9(6):984–994
5. Holdsworth F. Fractures, dislocations, and fracture-dislocations of the spine. J Bone Joint Surg Am 1970;52(8):1534–1551
6. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine 1983;8(8):817–831
7. McCormack T, Karaikovic E, Gaines RW. The load sharing classification of spine fractures. Spine 1994;19(15):1741–1744
8. Magerl F, Aebi M, Gertzbein SD, Harms J, Nazarian S. A comprehensive classification of thoracic and lumbar injuries. Eur Spine J 1994;3(4):184–201
9. Vaccaro AR, Lehman RA Jr, Hurlbert RJ, et al. A new classification of thoracolumbar injuries: the importance of injury morphology, the integrity of the posterior ligamentous complex, and neurologic status. Spine 2005;30(20):2325–2333
10. Vaccaro AR, Oner C, Kepler CK, et al; AOSpine Spinal Cord Injury & Trauma Knowledge Forum. AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. Spine 2013;38(23):2028–2037
11. Vu C, Gendelberg D. Classifications in brief: AO Thoracolumbar Classification System. Clin Orthop Relat Res 2020;478(2):434–440
12. Filgueira ÉG, Imoto AM, da Silva HEC, Meves R. Thoracolumbar burst fracture: McCormack load-sharing classification—systematic review and single-arm meta-analysis. Spine 2021;46(9): E542–E550
13. Srinivasan P. A review of thoracolumbar spine fracture classification systems. Indian Spine J 2018; 1(2):71–78
14. Moelmer M, Gehrchen M, Dahl B. Long-term functional results after short-segment pedicle fixation of thoracolumbar fractures. Injury 2013; 44(12):1843–1846
15. Aly TA. Short segment versus long segment pedicle screws fixation in management of thoracolumbar

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burst fractures: meta-analysis. Asian Spine J 2017; 11(1):150–160
16. Cankaya D, Balci M, Deveci A, Yoldas B, Tuncel A, Tabak Y. Better life quality and sexual function in men and their female partners with short-segment posterior fixation in the treatment of thoracolumbar junction burst fractures. Eur Spine J 2016;25(4):1128–1134
17. Youssef EM, Mohamed SH, Alsadek AA, Morsy AA. Short segment with index vertebra fixation versus long segment fixation in the management of thoracolumbar fractures. Egypt J Hosp Med 2023;90(1):1007–1013
18. McLain RF, Sparling E, Benson DR. Early failure of short-segment pedicle instrumentation for thoracolumbar fractures. A preliminary report. J Bone Joint Surg Am 1993;75(2):162–167
19. Wang H, Li C, Liu T, Zhao WD, Zhou Y. Biomechanical efficacy of monoaxial or polyaxial pedicle screw and additional screw insertion at the level of fracture, in lumbar burst fracture: An experimental study. Indian J Orthop 2012;46(4):395–401
20. Ouellet JA, Richards C, Sardar ZM, et al. Finite element analysis and biomechanical comparison of short posterior spinal instrumentation with divergent bridge construct versus parallel tension band construct for thoracolumbar spine fractures. Global Spine J 2013;3(2):85–94
21. Chokshi JJ, Shah M. Outcomes of including fracture level in short-segment fixation for thoracolumbar fracture dislocation. Asian Spine J 2019;13(1): 56–60
22. Dobran M, Nasi D, Brunozzi D, et al. Treatment of unstable thoracolumbar junction fractures: short-segment pedicle fixation with inclusion of the fracture level versus long-segment instrumentation. Acta Neurochir (Wien) 2016; 158(10):1883–1889
23. Gelb D, Ludwig S, Karp JE, et al. Successful treatment of thoracolumbar fractures with short-segment pedicle instrumentation. J Spinal Disord Tech 2010;23(5):293–301
24. Guven O, Kocaoglu B, Bezer M, Aydin N, Nalbantoglu U. The use of screw at the fracture level in the treatment of thoracolumbar burst fractures. J Spinal Disord Tech 2009;22(6):417–421
25. Jindal R, Jasani V, Sandal D, Garg SK. Current status of short segment fixation in thoracolumbar spine injuries. J Clin Orthop Trauma 2020;11(5):770–777
26. Sharif S, Shaikh Y, Yaman O, Zileli M. Surgical techniques for thoracolumbar spine fractures: WFNS spine committee recommendations. Neurospine 2021;18(4):667–680
27. Norton RP, Milne EL, Kaimrajh DN, Eismont FJ, Latta LL, Williams SK. Biomechanical analysis of four- versus six-screw constructs for short-segment pedicle screw and rod instrumentation of unstable thoracolumbar fractures. Spine J 2014; 14(8):1734–1739
28. Kose KC, Inanmaz ME, Isik C, Basar H, Caliskan I, Bal E. Short segment pedicle screw instrumentation with an index level screw and cantilevered hyperlordotic reduction in the treatment of type-A fractures of the thoracolumbar spine. Bone Joint J 2014;96-B(4):541–547
29. Joaquim AF, Maslak JP, Patel AA. Spinal reconstruction techniques for traumatic spinal injuries: a systematic review of biomechanical studies. Global Spine J 2019;9(3):338–347
30. Saad MM, Abdelhady AF, Bayomy EM. Short-segment posterior fixation with index level screws versus long-segment posterior fixation in thoracolumbar burst fracture. Adv Spine J 2022; 41(3): article 4
31. Luo ZW, Liao WJ, Sun BL, et al. Short-segment fixation and transpedicular bone grafting for the treatment of thoracolumbar spine fracture. Front Surg 2023;9:1039100
32. Mak SYJ, Siu YC, Chau WW, Lo CY, Ma CM. Long segment versus short segment stabilization in thoracolumbar spine fracture: a retrospective clinical and radiological analysis. J Orthop Trauma Rehabil 2023;30(1):22104917221128836
33. Wahba GM, Bhatia N, Bui CNH, Lee KH, Lee TQ. Biomechanical evaluation of short-segment posterior instrumentation with and without crosslinks in a human cadaveric unstable thoracolumbar burst fracture model. Spine 2010;35(3): 278–285
34. Alizadeh M, Kadir MRA, Fadhli MM, et al. The use of X-shaped cross-link in posterior spinal constructs improves stability in thoracolumbar burst fracture: a finite element analysis. J Orthop Res 2013;31(9):1447–1454
35. Wood KB, Li W, Lebl DR, Ploumis A. Management of thoracolumbar spine fractures. Spine J 2014;14(1):145–164
36. Hu X, Ma W, Chen J, Wang Y, Jiang W. Posterior short segment fixation including the fractured vertebra combined with kyphoplasty for unstable thoracolumbar osteoporotic burst fracture. BMC Musculoskelet Disord 2020;21(1):566

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37. P Oprel P, Tuinebreijer WE, Patka P, den Hartog D. Combined anterior-posterior surgery versus posterior surgery for thoracolumbar burst fractures: a systematic review of the literature. Open Orthop J 2010;4:93–100
38. Zhu Q, Shi F, Cai W, Bai J, Fan J, Yang H. Comparison of anterior versus posterior approach in the treatment of thoracolumbar fractures: a systematic review. Int Surg 2015;100(6):1124–1133
39. Khoo LT, Beisse R, Potulski M. Thoracoscopic-assisted treatment of thoracic and lumbar fractures: a series of 371 consecutive cases. Neurosurgery 2002;51(5, Suppl):S104–S117
40. Li X, Ma Y, Dong J, Zhou XG, Li J. Retrospective analysis of treatment of thoracolumbar burst fracture using mono-segment pedicle instrumentation compared with short-segment pedicle instrumentation. Eur Spine J 2012;21(10):2034–2042
41. Wei FX, Liu SY, Liang CX, et al. Transpedicular fixation in management of thoracolumbar burst fractures: monosegmental fixation versus short-segment instrumentation. Spine 2010; 35(15):E714–E720
42. Xu G, Fu X, Du C, et al. Biomechanical comparison of mono-segment transpedicular fixation with short-segment fixation for treatment of thoracolumbar fractures: a finite element analysis. Proc Inst Mech Eng H 2014;228(10):1005–1013
43. Altay M, Ozkurt B, Aktekin CN, Ozturk AM, Dogan O, Tabak AY. Treatment of unstable thoracolumbar junction burst fractures with short- or long-segment posterior fixation in Magerl type a fractures. Eur Spine J 2007;16(8):1145–1155
44. Tezeren G, Bulut O, Tukenmez M, Ozturk H, Oztemur Z, Ozturk A. Long segment instrumentation of thoracolumbar burst fracture: fusion versus nonfusion. J Back Musculoskelet Rehabil 2009;22(2):107–112
45. Baaj AA, Reyes PM, Yaqoobi AS, et al. Biomechanical advantage of the index-level pedicle screw in unstable thoracolumbar junction fractures. J Neurosurg Spine 2011;14(2):192–197
46. Kasliwal MK, Shaffrey CI, Lenke LG, Dettori JR, Ely CG, Smith JS. Frequency, risk factors, and treatment of distal adjacent segment pathology after long thoracolumbar fusion: a systematic review. Spine 2012;37(22, Suppl):S165–S179
47. Avanzi O, Landim E, Meves R, Caffaro MF, de Albuquerque Araujo Luyten F, Faria AA. Thoracolumbar burst fracture: load sharing classification and posterior instrumentation failure. Rev Bras Ortop 2015;45(3):236–240
48. Ituarte F, Wiegers NW, Ruppar T, Goldstein C, Nourbakhsh A. Posterior thoracolumbar instrumented fusion for burst fractures: a meta-analysis. Clin Spine Surg 2019;32(2):57–63
49. McClelland S III, Goldstein JA. Minimally invasive versus open spine surgery: what does the best evidence tell us? J Neurosci Rural Pract 2017;8(2): 194–198
50. Carazzo CA, Yurac R, Guiroy A, Zamorano JJ, Cabrera JP, Joaquim AF; AO Spine Latin America Trauma Study Group. Minimally invasive versus open surgery for the treatment of types B and C thoracolumbar injuries: a PRISMA systematic review. Int J Spine Surg 2021;15(4):803–810
51. Wang H, Zhou Y, Li C, Liu J, Xiang L. Comparison of open versus percutaneous pedicle screw fixation using the Sextant system in the treatment of traumatic thoracolumbar fractures. Clin Spine Surg 2017;30(3):E239–E246
52. Lee YS. Long-term follow-up results of short-segment posterior screw fixation for thoracolumbar burst fractures. J Korean Neurosurg Soc 2004;37(6):416–421
53. Kim HS, Park SK, Joy H, Ryu JK, Kim SW, Ju CI. Bone cement augmentation of short segment fixation for unstable burst fracture in severe osteoporosis. J Korean Neurosurg Soc 2008;44(1):8–14
54. Lin HH, Chang MC, Wang ST, Liu CL, Chou PH. The fates of pedicle screws and functional outcomes in a geriatric population following polymethylmethacrylate augmentation fixation for the osteoporotic thoracolumbar and lumbar burst fractures with mean ninety five month follow-up. Int Orthop 2018;42(6):1313–1320
55. Lai O, Zhang X, Hu Y, et al. Long-segment fixation VS short-segment fixation combined with kyphoplasty for osteoporotic thoracolumbar burst fracture. BMC Musculoskelet Disord 2022; 23(1):160
56. National Spine Health Foundation. The Smoking Spine. Published January 25, 2023. Accessed September 11, 2024 at: https://spinehealth.org/article/the-smoking-spine/
57. Broz K, Walk RE, Tang SY. Complications in the spine associated with type 2 diabetes: the role of advanced glycation end-products. Med Novel Technol Devices 2021;11:100065

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19 Controversies About ACM Surgery

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Introduction

Controversies are part and parcel of medicine. The Oxford dictionary defines controversy as a "public discussion and disagreement." The word may have a different connotation in the common parlance but in science, it denotes a thriving scientific quest and an ongoing discovery of new information. As the new knowledge and inventions question our existing beliefs, the scientific community inevitably bifurcates into two groups: the believers and the sceptics. This is what typifies a controversy, which continues until the time when the long-held practice is changed forever, or it dies down due to its inability to hold ground. A few, however, linger on. When we talk about controversies in neurosurgery, the Chiari malformation finds its mention right up there.

Arnold-Chiari malformation (ACM), more frequently referred to as Chiari malformations nowadays, encompasses a group of malformations of the posterior fossa and hindbrain with or without other associated intracranial or extracranial anomalies.[1–3] Several types of this malformation have been described with varying extent of congenital defects. For this chapter, we shall confine ourselves to the most common of these malformations, the type 1 Chiari malformation (C1M). C1M is by far the most common of these malformations with an incidence of 0.24 to 0.9% in adults and 0.8 to 3.7% in children, with a mean value of 0.6 to 0.9% in the entire population.[4] In this malformation, the cerebellar tonsils prolapse below the foramen magnum (FM), leading to an overcrowding of structures at the largest outlet of the cranium.[5,6]

The Consensus

Let us first discuss issues where neurosurgeons have largely reached a consensus. C1M is a neurodevelopmental mesenchymal error with a disproportionately small posterior fossa and a volume mismatch for the contents, i.e., the hindbrain.[7–10] The resultant overcrowding of the structures and blockade of cerebrospinal fluid (CSF) flow at the FM get accentuated by the normal cranial pulsations and not only produce compressive symptoms but also lead to syringomyelia, the most dramatic effect of C1M. The craniovertebral junction (CVJ) instability theory of Professor Atul Goel has, however, challenged the existing theories.[5,6] Nevertheless, the surgical target is uniformly agreed to be the FM, even at the time of a symptomatic recurrence. There is also a clear consensus that surgical treatment is indicated only for the symptomatic patients. Once a decision to intervene has been made, the key consideration is to rule out a CVJ instability and "complex radiological features" on the preoperative imaging. In the pure C1M, both bony and dural decompressions (posterior fossa decompression [PFD] and posterior fossa decompression with duraplasty, PFDD respectively) are commonplace and effective. However, the indication of each remains to be crystallized. What has been consistently shown in the literature is that, as the

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extent of PFD increases, so does the clinical improvement with the caveat of an increased risk of complications.[11] Although controversies surround the extent of decompression, everyone agrees that the bony decompression must be appropriately sized and C2 laminectomy should be avoided. Irrespective of the method employed, the current surgical strategies are highly effective in most of the patients. There are, however, some patients who continue to remain symptomatic even after surgery. In the next segment, we shall try to get into the details of some of these unsettled issues.

The Controversies

Considering the limitation of time and space, the authors wish to focus on the following few important issues:

- What do we, as surgeons, aim to rectify? The altered anatomy or an altered physiology?
- Should we treat all symptomatic patients and those with a syrinx even when asymptomatic, or do we need to be more selective?
- What to do? Should we stop at bony decompression or go beyond? If we go beyond, what works best —dural scoring or duraplasty or tonsillar resection?
- What leads to postoperative nonimprovement and persistent syringomyelia and how to treat them?

What Are We Aiming to Rectify Surgically? The Altered Anatomy or the Altered Physiology?

The issue pertains to both, the C1M with syrinx as well as the lesser common manifestation of hydrocephalus. The anatomical theory, i.e., an instability being the root cause of the epiphenomenon of tonsillar ectopia in C1M, was proposed by Professor Atul Goel. Through his vast experience and several publications in reputed journals, Professor Goel has been able to consistently prove that C1–C2 fusion benefits a large majority of these patients, which lends credence to his postulation that a central atlanto-axial instability is the mother of all manifestations of CVJ anomaly, including the pure soft tissue variant. The tonsillar herniation is a protective epiphenomenon in this theory and PFD can potentially deflate this natural airbag with counterproductive results. Goel,[12] in a retrospective study, reported his experience and outcomes for 65 patients with C1M who had undergone only fusion surgery. The results revealed that 63 of 65 patients (96.9%) showed improvement. Thus, the culprit appears to be anatomical here. The development of and increase/sustenance of C1M-associated syringomyelia has been explained over the years. Although all theories pin the blame on the tonsillar impaction at the FM, the theories of syrinx development vary, some ascribing it to a raised intracranial CSF pressure[13] while some theories implicate a spinal subarachnoid CSF hypertension.[14]

The presence of hydrocephalus in C1M is also equally intriguing and influences the management decisions. Diagnosed either before or after a PFD, the incidence of hydrocephalus in C1M is thought to be around 10%.[15,16] What produces hydrocephalus? An altered anatomy or an altered physiology? Is hydrocephalus in C1M a cause or an effect? This has implication in that the common belief of treatment of hydrocephalus, either using a ventriculoperitoneal shunting or an endoscopic third ventriculostomy, producing a “one stone two bird effect” may not be true always.[17,18] The “pressure from above” theory leading to crowding of structures at the FM stemmed from findings of the original description of this malformation by Hans Chiari back in 1891.[19] The subsequent theories proposed by Williams[20] and Gardner[7] also supported this hypothesis. Hydrocephalus is a cause

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of C1M in this narrative and the treatment of hydrocephalus as the first step makes sense. Additionally, an upfront CSF diversion provides relief of headache, potential reversal of tonsillar ectopia and syringomyelia, and if eventually a surgical decompression is needed, a protection against the postoperative pseudomeningocele.

The alternate theory, namely, the hydrocephalus being secondary to C1M, was proposed in 1931 by the Dutch surgeon van Houweninge Graftdijk.[21] He hypothesized that the crowding of structures blocks the fourth ventricular outflow tract which results in CSF flow obstruction and hydrocephalus. Thus, the primary problem is more of an anatomical origin and hydrocephalus is an effect. The heightened hydrodynamic pulsation to drive CSF through narrow passages (foramina of Luschka) further impedes CSF absorption. Thus, the anatomical obstruction leads to a physiologic dysfunction. In this "an effect rather than a cause" narrative, the treatment of the C1M should take care of both. The third emerging theory is that C1M and hydrocephalus may be co-associations, both arising due to jugular venous stenosis with reduced CSF absorption.[22] The build-up of CSF pressure causes C1M by a cranio-caudal pressure gradient and simultaneously a hydrocephalus due to improper CSF absorption. This explains why some patients require a PFD even after a shunt or even worsen following a shunt surgery.

Should We Treat All Symptomatic Patients and All Patients With a Syrinx, or Do We Need to Be More Selective?

Considering that around 15 to 20% of the patients continue to remain symptomatic after surgery,[23] inappropriate case selection being one of the causes, we must choose our cases well. To this end, we need to understand the symptoms that respond well to the treatment and those which do not. Several preoperative scoring systems have been advised.[24,25] Symptoms like muscle atrophy, ataxia, peripheral neuropathy, dorsal column dysfunction etc. are predictors of poor postoperative outcomes. Dyste et al[26] noted that a model based on the triad of atrophy, ataxia, and scoliosis allowed prediction of long-term outcome at 95% confidence interval. More recently, Greenberg et al[24] proposed the Chiari Severity Index. They categorized the preoperative symptoms and presence/size of syrinx based on how the patients eventually fared after surgery and finally proposed a grading system comprising different symptomatology and syringomyelia. This grading predicted the likelihood improvement after a decompressive surgery. Grade 1 patients are those who have classic Chiari headache or nonlocalized headache with either no syrinx or <6 mm wide syrinx. Approximately 83% of these patients can be expected to have good outcomes after surgery. Grade 2 patients are those who have either frontotemporal headache or no headache and have myelopathic signs with or without a syrinx (<6 mm). Around 69% of these patients can be expected to have favorable postoperative outcomes. On the other hand, patients with either frontotemporal headache or no headache and have myelopathic signs and an advanced syrinx of >6 mm have only 45% chance of improvement and are categorized as grade 3. Based on their findings, they proposed this index to aid in patient selection. As per this system, the more severe the syrinx, the less are the chances of improvement. Having said that, the consensus of international experts advises otherwise. A high degree of agreement was present among the experts[23] on the advocacy of surgery in CM1 with Syr (CM1-A), especially in young people, in case of (1) holocord Syr; (2) evolutionary trend (clinical/MRI worsening); (3) central syrinx with Vaquero Index >0.5 or eccentric syrinx; and (4) Syr-SB.

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What to Do? Should We Stop at Bony Decompression or Go Beyond? If so, What Works Best? Dural Scoring or Duraplasty or Tonsillar Resection? What Is the Role of Posterior Fixation in C1M?

Although it is agreed upon that symptomatic patients should be offered surgery, the exact nature and extent of the surgery, however, still remains a matter of debate. The treatment strategies range from a simple posterior fossa bony decompression to an extensive intradural exploration with tonsillar resection (posterior fossa decompression with resection of tonsils, PFDRT) and even a posterior fixation (PF).

Bony versus dural decompression: Chai et al[26] in 2018 reported the largest meta-analysis of 3666 patients with C1M and found that the resolution of syringomyelia was better at the cost of a higher incidence of CSF leak and aseptic meningitis in the dural decompression group. A study by Forander et al in 2014[27], showed the addition of a duraplasty leads to a significant decrease in the reoperation rates related to clinical nonimprovement (2% vs. 8%) but at the cost of a higher CSF-related complications (7% vs. 0%). Massimi et al,[28] in another meta-analysis including both adults and children, noted that PFD was sufficient in children without a syringomyelia while PFDD was the procedure of choice in adults or in large syringomyelia irrespective of age. In our own experience published recently,[29] PFD only is as effective as dural decompression, albeit with a much lesser complication. The recently published consensus guidelines[30] from the Congress of Neurological Surgeons emphasized the lack of strong evidence in this regard and recommended that both procedures (PFD and PFDD) remain valid choices in symptomatic cases (level C). **Figs. 19.1** and **19.2** show examples of PFD and PFDD in C1M.

How extensive should one be once the dura is opened—dural scoring or arachnoid-preserving duraplasty or tonsillar resection? The intradural procedures like tonsillar shrinkage or resection, opening of the obex etc. aim to eliminate all possible reasons of CSF outflow obstruction. Those in favor of an intradural procedure advise tonsillar resection if the tonsils are displaced up to or beyond C2. They advise division of arachnoid bands and exploration of the foramen of Magendie at the same time. Their logic is that the first surgery is the best time to deal with all problems at one go. They have shown an early and more complete syringomyelia resolution with a low incidence of re-surgery.[28,32] Those against this policy argue that subarachnoid surgical manipulations promote surgical scarring which in turn leads to iatrogenic CSF flow interruptions.[28,29] They advise a subarachnoid procedure only during a re-exploration for a postoperative nonimprovement. Chai et al[27] noted a better clinical and radiological outcome with PFDRT as compared to PFDD. They also noted a particular improvement in nonpain and functional components of the objective Chicago Chiari Outcome Scale (CCOS) after PFDRT. Antkowiak and Tabakow,[33] in a recent meta-analysis, found that both PFDD and PFDRT were superior to PFD, especially in patients with syringomyelia–Chiari complex because of a greater syringomyelia reduction (RR, 1.23; 95% CI, 1.09–1.39 and RR, 1.32; 95% CI, 1.15–1.51, respectively) and a better clinical improvement (RR, 1.24; 95% CI, 1.10–1.39 and RR, 1.24; 95% CI, 1.08–1.44, respectively). Complications were found to be maximum in the PFDD group (3.8 times higher odd for CSF leak and 8.3 times higher odd of neurological deficits). They did not, however, find any differences between PFDD and PFDRT. They concluded that both PFDD and PFDRT could be considered equally efficient. The systematic review by Zhao et al,[34] on the other hand,

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Fig. 19.1 Preoperative and postoperative images of a patient with pure Chiari malformation where only posterior fossa decompression (PFD) was done. Preoperative MRI **(a)** is suggestive of tonsillar descent with cervical syrinx. CT images sagittal **(b)** and coronal **(c)** sections show no craniovertebral junction (CVJ) instability. The patient underwent PFD following which postoperative MRI **(d)** showed resolution of syrinx.

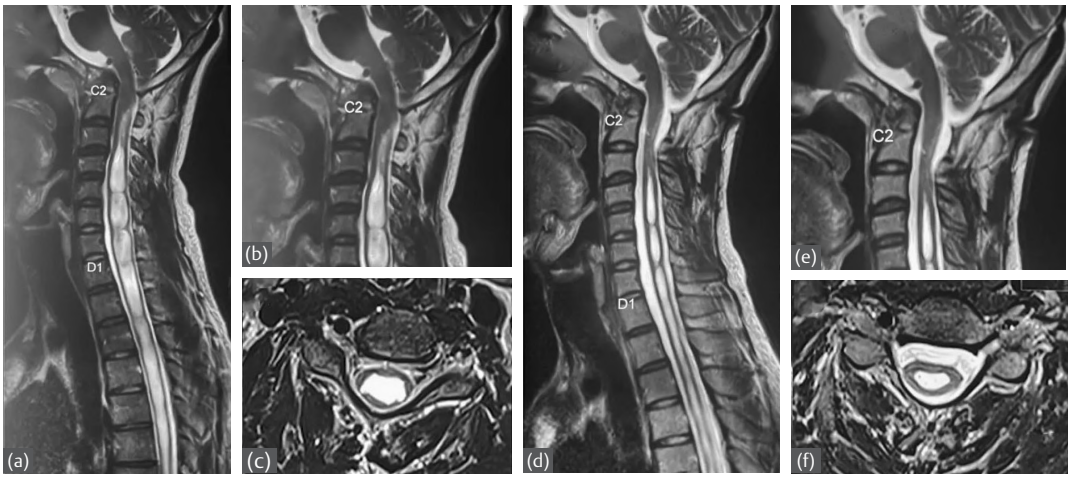

Fig. 19.2 Preoperative and postoperative images of a case of pure Chiari malformation, where the patient underwent posterior fossa decompression with duroplasty (PFDD). **(a–c)** Preoperative images of the patient with Chiari malformation with extensive cervicodorsal syrinx. The patient underwent PFDD following which there was reduction in the size of syrinx on postoperative MRI images **(d–f)**.

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showed a very high complication rate (52%) in PFDRT compared to the PFDD group (21%). However, Jia et al[35] did not find the increased incidence of complication in PFDRT to be statistically significant (47% vs. 35%). Therefore, to strike a balance between the pros and cons of intradural manipulations, some intermediate solutions have been reported that includes only an arachnoid-preserving expansive duraplasty, scoring of the outer layer of the craniocervical junctional dura, and utilization of ultrasound to guide the procedure. A meta-analysis on the dura scoring technique by Chang et al[36] did not find the dural scoring any inferior to PFDD on parameters like clinical improvement, syringomyelia improvement, and reoperation. Dural splitting technique had shorter operation durations (p = 0.0007), a shorter length of stay (p = 0.0007), and a shorter overall postoperative complication (p < 0.0001), especially CSF leak (p = 0.005), meningitis (p = 0.002), and pseudomeningocele (p = 0.002). Considering the pros and cons of dural opening, intraoperative image guidance like ultrasound and MRI for decision-making has been suggested.[37] Reported studies largely point towards an advantage but large comparative data are missing.

Decompression or fusion? Before discussing this issue, it is imperative to understand the three ways in which C1M may present to a neurosurgeon, namely, a pure C1M, a complex C1M, and C1M with evident instability like a basilar invagination with or with a co-existent atlanto-axial dislocation. The latter two situations unequivocally require additional procedures including a posterior fusion. **Fig. 19.3** shows these three situations.

Complex Chiari malformation (CCM)[38] has been defined using various criteria, the commonality being the additional presence of certain soft tissue (like the obex lying below the FM and a medullary kink) and bony abnormalities (type 2 basilar invagination, ventral compression of the spinal cord by an abnormally retroflexed odontoid, and acute clivo-cervical angulation) with the C1M findings. Recognition of these "complex" factors is essential because a simple PFD alone or with a duraplasty (PBDD) may fail to improve the symptoms. Bollo et al,[39] in a multivariate analysis, found three factors, namely, CM1.5, basilar invagination, and clivo-cervical angle (CXA) <125 degrees, to be significantly associated with the requirement of a delayed occipito-cervical fusion (OCF). Recently, Ali Turabi et al[40] from India published their experience with CCM and noted a significant difference between fusion (92.3% improvement) and nonfusion groups (46.2% improvement). **Fig. 19.4** shows a case of CCM.

The need for fusion in frank CVJ anomaly is beyond any doubt. In this regard, a study from our own institution[41] back in 2007 showed that 70% of the patients with a missed CVJ instability who underwent a simple PFD eventually required a fusion. In the contemporary times, these are rarely missed preoperatively and hence treated appropriately.

Coming to the real controversial issue of fusion as the only treatment in pure C1M, Dr Atul Goel,[12] in a series of 65 patients treated with atlanto-axial fusion, first coined the term central atlanto-axial instability in 2015. He stated that these patients have no obvious preoperatively demonstrable instability but respond to a fusion surgery. He postulated that basilar invagination, C1M, and syringomyelia had a common origin from CVJ instability. In a more homogenous group of 57 patients (C1M without any bony abnormality), he demonstrated in 2019, a sustained clinical improvement in all patients and a syrinx resolution in nearly 50% of the patients.[5] Several authors, with their own data and literature reviews, have, however, questioned this theory. Salunke et al,[42] in a prospective study of 40 patients with type 1 Chiari malformation treated with C1–C2 fusion alone, reported an improvement in 28 (70%) patients. They proposed that the improvement may be the result of an indirect vertical decompression

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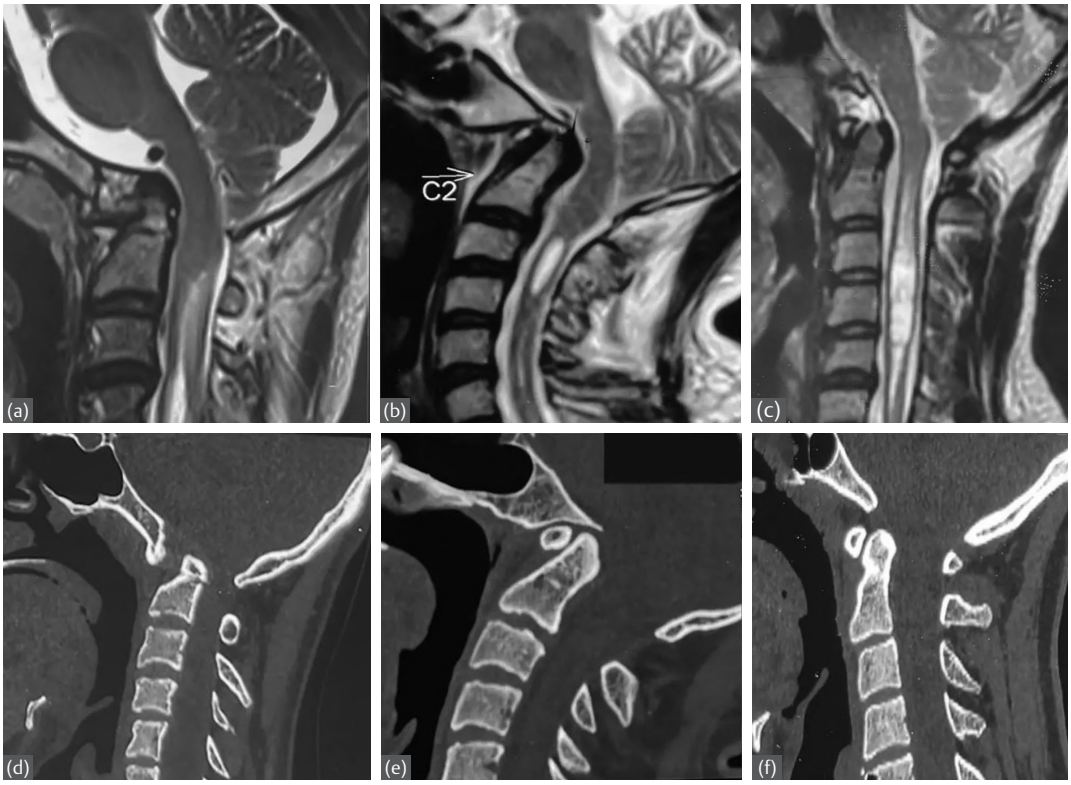

Fig. 19.3 Preoperative MRI and CT images of three patterns of presentation of type 1 Chiari malformation (CM 1). **(a, d)** MRI and CT images of tonsillar herniation associated with increased atlantoaxial dislocation with basilar invagination but without any ventral brainstem compression. **(b, e)** MRI and CT images of complex Chiari malformation with ventral brainstem compression and associated cervical syrinx. **(c, f)** MRI and CT images of pure Chiari I malformation with tonsillar herniation and cervical syrinx without any associated craniovertebral junction (CVJ) instability.

resulting from the distraction, rather than fusion per se. In our own experience[30] the only study so far to compare the three methods of treatment (PBD, PFDD, and posterior fusion, PF) in a cohort of C1M without any bony instability, we have shown that the long-term outcomes after PF are no different than the other procedures. Regarding the level of fusion, whenever planned, both C1–C2 and OCFs are used.[43-45] The fact that many of these patients have an assimilated atlas where a C1 screw essentially includes the occiput as well and dissection of the C1–C2 joints may be difficult in some cases, an OCF also remains a valid surgical option.[44,45]

Postoperative Nonimprovement: How to Proceed?

Before we delve deeper into yet another piece of unsettled puzzle, we must understand that the nonimprovement may be due to the surgical oversight like inaccurate patient selection and technical errors or a disease progression. These are usually due to patient factors like undetected comorbidities such as CVJ instability and intracranial hypertensions (craniosynostosis or idiopathic), complex bony and soft tissue anatomy (complex Chiari), tonsillar ectopia below C2, and the pediatric age group.[46]

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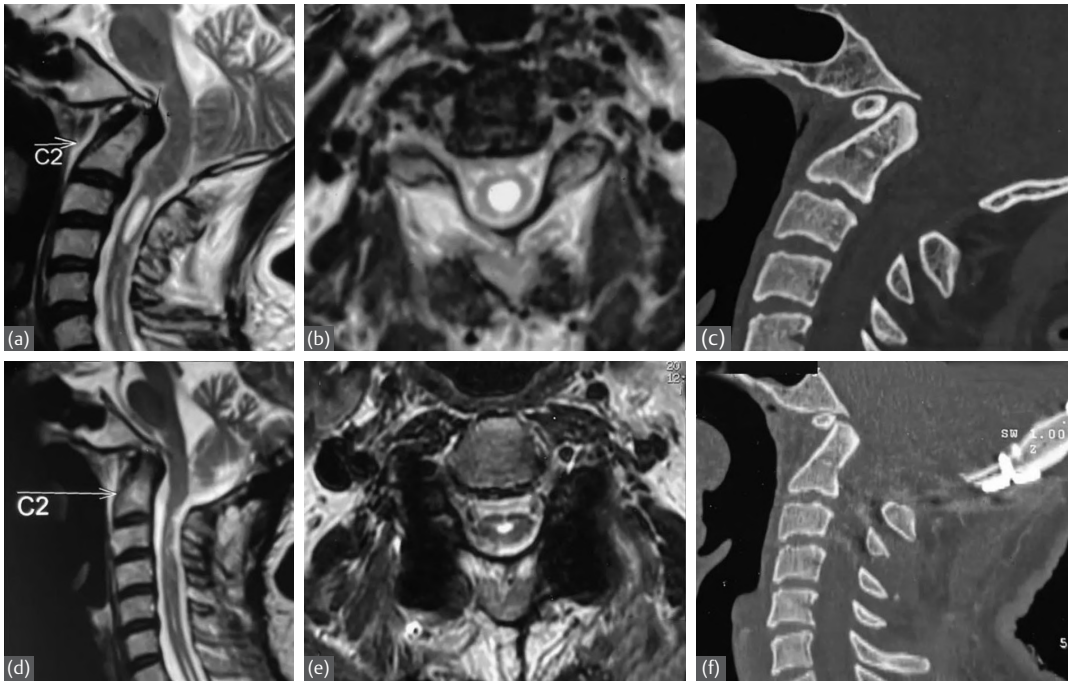

Fig. 19.4 Preoperative and postoperative images of a patient with complex Chiari malformation. Preoperative images show an acute clivo-cervical angle, confirmed on CT with a large syrinx with tonsillar ectopia **(a–c)**. The patient underwent posterior fossa decompression (PFD) with occipitocervical fixation. Postoperative images showing improvement in clivo-cervical angle and resolution of cervical syrinx **(d–f)**.

The important questions are: when and how to declare a failure and how to proceed? Postoperative deterioration is usually due to a missed instability or hydrocephalus. Therefore, prompt postoperative imaging of the brain and the CVJ will allow corrective steps to be taken. On the other hand, persistent symptoms with or without C1M features and/or syringomyelia persisting beyond 6-12 months can be considered as a treatment failure. It is important to note that clinical failure (no improvement is symptoms) can be declared earlier, 6-12 months from surgery, while a period of waiting for 12-24 months is advisable to declare a radiological failure. A very high degree of agreement was obtained on this cut off time in the international consensus document published by Massimi, et al.[11] Level 2 evidence is available on this in the Congress of Neurological Surgeons statement published by Pattisapu, *et al* as well.[31] Persistence of a collapsed syrinx with symptomatic improvement is, however, not considered a treatment failure.

In the event of a treatment failure, a decision to reoperate must consider two contrasting possibilities: the myelopathic symptoms rarely improve and certain symptoms can spontaneously improve, underscoring the scope of a wait and watch policy in some of these cases. For rest of the patients, most authors advocate a resurgery at the FM while there are a few others who prefer a direct treatment of the syrinx.[47] Klekamp[48] advises a thorough workup including a cine MRI of the FM and a re-exploration with an intent of minimal intradural arachnoid release, with no manipulation of thick arachnoidal

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scars near the foramen of Magendie, and they discourage a fourth ventricular shunting. A capacious duraplasty is advised and with this policy, they reported favorable outcomes in 66% of the patients at 5 years. Maintaining a stand diagonally opposite to this, Soleman et al[49] reported the largest study on syringo-subarachnoid shunt (SSS) for persistent syringomyelia after C1M decompression. They reported 11.8% improvement in the functional score and nearly 76% reduction is syrinx size. They not only recommend an SSS as the treatment of choice for persistent syrinx but also go a step further in advocating a simultaneous SSS at the time of index Chiari decompression in patients with a holocord syrinx. Their argument is that a redo surgery at the scarred FM can be counterproductive with the potential for higher complications and high failure rates.

The Pragmatic Approach

The authors, based on their own philosophy, experience, and a review of the recent literature, recommend a pragmatic approach as shown in the algorithm (**Fig. 19.5**).

Conclusion

C1M remains a controversial topic. Notwithstanding our evolving understanding, the currently available literature does allow formulation of practical management strategies. The need of the hour is for multi-institutional collaborations and randomized controlled trials. Also, a uniformity in reporting patient outcomes will bring a much-needed coherence in the literature. Hopefully, we can put to rest many of the controversies in the not-so-distant future.

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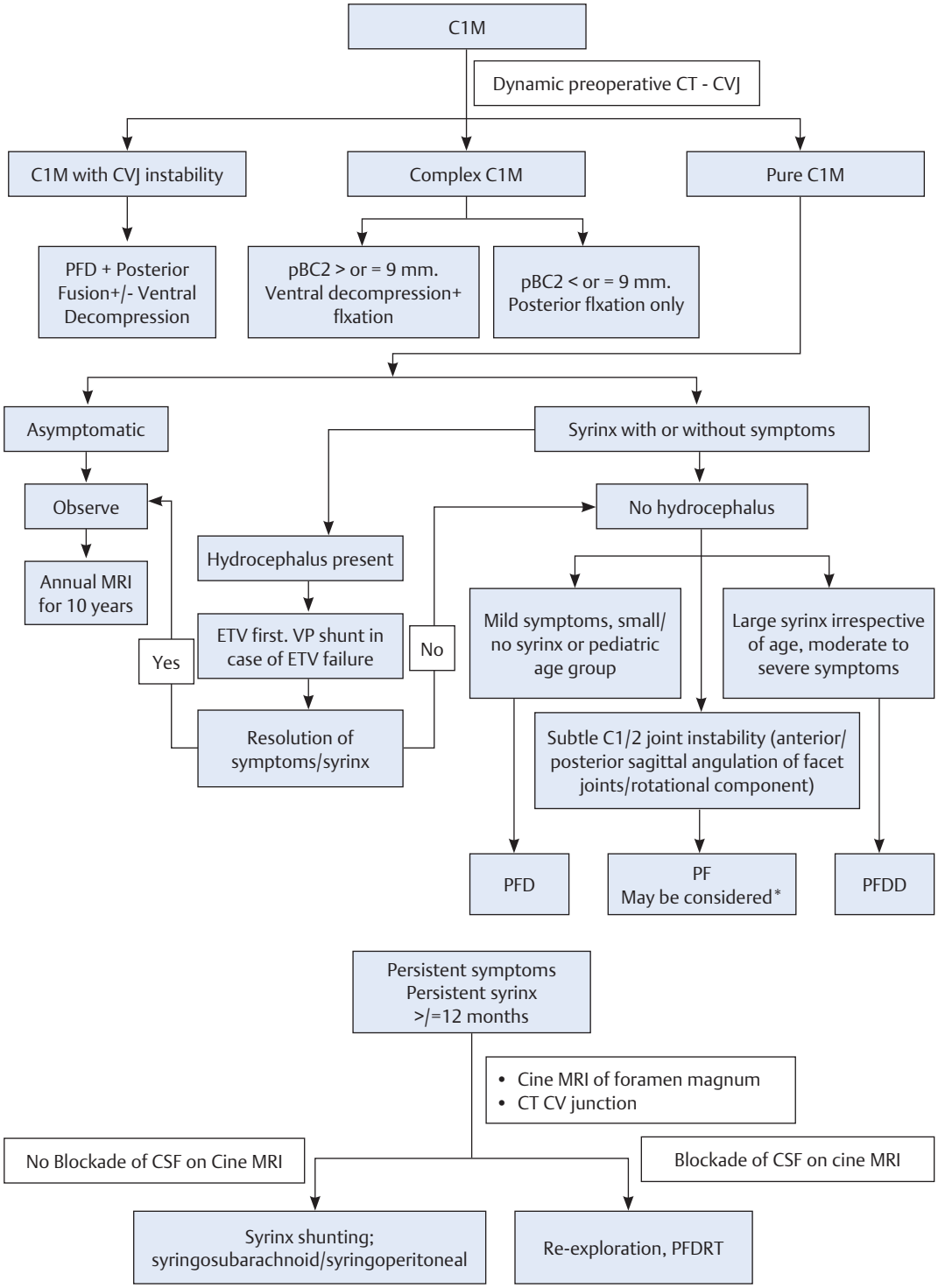
C1M
Dynamic preoperative CT - CVJ
C1M with CVJ instability
Complex C1M
Pure C1M
PFD + Posterior Fusion+/- Ventral Decompression
pBC2 > or = 9 mm. Ventral decompression+ flxation
pBC2 < or = 9 mm. Posterior flxation only
Asymptomatic
Syrinx with or without symptoms
Observe
Annual MRI for 10 years
Yes
Hydrocephalus present
ETV first. VP shunt in case of ETV failure
Resolution of symptoms/syrinx
No
No hydrocephalus
Mild symptoms, small/ no syrinx or pediatric age group
Large syrinx irrespective of age, moderate to severe symptoms
Subtle C1/2 joint instability (anterior/ posterior sagittal angulation of facet joints/rotational component)
PFD
PF May be considered*
PFDD
Persistent symptoms Persistent syrinx >/=12 months
• Cine MRI of foramen magnum
• CT CV junction
No Blockade of CSF on Cine MRI
Blockade of CSF on cine MRI
Syrinx shunting; syringosubarachnoid/syringoperitoneal
Re-exploration, PFDRT

Fig. 19.5 A suggested management algorithm.

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References

1. de Arruda JA, Figueiredo E, Monteiro JL, Barbosa LM, Rodrigues C, Vasconcelos B. Orofacial clinical features in Arnold Chiari type I malformation: a case series. J Clin Exp Dent 2018;10(4):e378–e382
2. Bhimani AD, Esfahani DR, Denyer S, et al. Adult Chiari I malformations: an analysis of surgical risk factors and complications using an international database. World Neurosurg 2018;115:e490–e500
3. Kandeger A, Guler HA, Egilmez U, Guler O. Major depressive disorder comorbid severe hydrocephalus caused by Arnold-Chiari malformation. Indian J Psychiatry 2017;59(4):520–521
4. Holste KG, Muraszko KM, Maher CO. Epidemiology of Chiari I malformation and syringomyelia. Neurosurg Clin N Am 2023;34(1):9–15
5. Goel A, Kaswa A, Shah A. Atlantoaxial fixation for treatment of Chiari formation and syringomyelia with no craniovertebral bone anomaly: report of an experience with 57 cases. Acta Neurochir Suppl (Wien) 2019;125:101–110
6. Goel A. Is Chiari malformation nature's protective "air-bag"? Is its presence diagnostic of atlantoaxial instability? J Craniovertebr Junction Spine 2014; 5(3):107–109
7. Gardner WJ. Hydrodynamic mechanism of syringomyelia: its relationship to myelocele. J Neurol Neurosurg Psychiatry 1965;28(3):247–259
8. McLone DG, Knepper PA. The cause of Chiari II malformation: a unified theory. Pediatr Neurosci 1989;15(1):1–12
9. Buell TJ, Heiss JD, Oldfield EH. Pathogenesis and cerebrospinal fluid hydrodynamics of the Chiari I malformation. Neurosurg Clin N Am 2015;26(4):495–499
10. Stovner LJ, Bergan U, Nilsen G, Sjaastad O. Posterior cranial fossa dimensions in the Chiari I malformation: relation to pathogenesis and clinical presentation. Neuroradiology 1993;35(2):113–118
11. Massimi L, Peretta P, Erbetta A, et al; International Experts - Jury of the Chiari & Syringomyelia Consensus Conference, "Milan, November 11–13, 2019". Diagnosis and treatment of Chiari malformation type 1 in children: the International Consensus Document. Neurol Sci 2022;43(2): 1311–1326
12. Goel A. Is atlantoaxial instability the cause of Chiari malformation? Outcome analysis of 65 patients treated by atlantoaxial fixation. J Neurosurg Spine 2015;22(2):116–127
13. Heiss JD, Patronas N, DeVroom HL, et al. Elucidating the pathophysiology of syringomyelia. J Neurosurg 1999;91(4):553–562
14. Oldfield EH, Muraszko K, Shawker TH, Patronas NJ. Pathophysiology of syringomyelia associated with Chiari I malformation of the cerebellar tonsils. Implications for diagnosis and treatment. J Neurosurg 1994;80(1):3–15
15. Tubbs RS, Beckman J, Naftel RP, et al. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation Type I. J Neurosurg Pediatr 2011;7(3):248–256
16. Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery 1999;44(5):1005–1017
17. Hoffman HJ, Tucker WS. Cephalocranial disproportion. A complication of the treatment of hydrocephalus in children. Childs Brain 1976;2(3):167–176
18. Caldarelli M, Novegno F, Di Rocco C. A late complication of CSF shunting: acquired Chiari I malformation. Childs Nerv Syst 2009;25(4): 443–452
19. Chiari H: Ueber Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. Dtsch Med Wochenscriff 17:1172–1175, 1891
20. Williams H. A unifying hypothesis for hydrocephalus, Chiari malformation, syringomyelia, anencephaly and spina bifida. Cerebrospinal Fluid Res 2008;5:7
21. Mortazavi MM, Tubbs RS, Hankinson TC, Pugh JA, Cohen-Gadol AA, Oakes WJ. The first posterior fossa decompression for Chiari malformation: the contributions of Cornelis Joachimus van Houweninge Graftdijk and a review of the infancy of "Chiari decompression." Childs Nerv Syst 2011;27(11):1851–1856
22. Koyanagi I, Houkin K. Pathogenesis of syringomyelia associated with Chiari type 1 malformation: review of evidences and proposal of a new hypothesis. Neurosurg Rev 2010;33(3):271–284, discussion 284–285
23. Schijman E, Steinbok P. International survey on the management of Chiari I malformation and syringomyelia. Childs Nerv Syst 2004;20(5): 341–348
24. Greenberg JK, Yarbrough CK, Radmanesh A, et al. The Chiari Severity Index: a preoperative grading system for Chiari malformation type 1. Neurosurgery 2015;76(3):279–285, discussion 285

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25. Aliaga L, Hekman KE, Yassari R, et al. A novel scoring system for assessing Chiari malformation type I treatment outcomes. Neurosurgery 2012; 70(3):656–664, discussion 664–665
26. Dyste GN, Menezes AH, VanGilder JC. Symptomatic Chiari malformations. An analysis of presentation, management, and long-term outcome. J Neurosurg 1989;71(2):159–168
27. Chai Z, Xue X, Fan H, et al. Efficacy of posterior fossa decompression with duraplasty for patients with Chiari malformation type I: a systematic review and meta-analysis. World Neurosurg 2018;113: 357–365.e1
28. Förander P, Sjåvik K, Solheim O, et al. The case for duraplasty in adults undergoing posterior fossa decompression for Chiari I malformation: a systematic review and meta-analysis of observational studies. Clin Neurol Neurosurg 2014;125:58–64
29. Massimi L, Frassanito P, Chieffo D, Tamburrini G, Caldarelli M. Bony decompression for Chiari malformation type i: long-term follow-up. Acta Neurochir Suppl (Wien) 2019;125:119–124
30. Rangari K, Das KK, Singh S, et al. Type I Chiari malformation without concomitant bony instability: assessment of different surgical procedures and outcomes in 73 patients. Neurospine 2021;18(1):126–138
31. Pattisapu JV, Ackerman LL, Infinger LK, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines for patients with Chiari malformation: surgical interventions. Neurosurgery 2023;93(4):731–735
32. Lin W, Duan G, Xie J, et al. Comparison of results between posterior fossa decompression with and without duraplasty for the surgical treatment of Chiari malformation type I: a systematic review and meta-analysis. World Neurosurg 2018;110: 460–474.e5
33. Antkowiak L, Tabakow P. Comparative assessment of three posterior fossa decompression techniques and evaluation of the evidence supporting the efficacy of syrinx shunting and filum terminale sectioning in Chiari malformation type I. A systematic review and network meta-analysis. World Neurosurg 2021;152:31–43
34. Zhao JL, Li MH, Wang CL, Meng W. A systematic review of Chiari I malformation: techniques and outcomes. World Neurosurg 2016;88:7–14
35. Jia C, Li H, Wu J, et al. Comparison decompression by duraplasty or cerebellar tonsillectomy for Chiari malformation-I complicated with syringomyelia. Clin Neurol Neurosurg 2019;176:1–7
36. Chang TW, Zhang X, Maoliti W, Yuan Q, Yang XP, Wang JC. Outcomes of dura splitting decompression versus posterior fossa decompression with duraplasty in the treatment of Chiari I malformation: a systematic review and meta-analysis. World Neurosurg 2021;147:105–114
37. Fan T, Zhao H, Zhao X, Liang C, Wang Y, Gai Q. Surgical management of Chiari I malformation based on different cerebrospinal fluid flow patterns at the cranial-vertebral junction. Neurosurg Rev 2017;40(4):663–670
38. Brockmeyer DL, Spader HS. Complex Chiari malformations in children: diagnosis and management. Neurosurg Clin N Am 2015;26(4):555–560
39. Bollo RJ, Riva-Cambrin J, Brockmeyer MM, Brockmeyer DL. Complex Chiari malformations in children: an analysis of preoperative risk factors for occipitocervical fusion. J Neurosurg Pediatr 2012;10(2):134–141
40. Asghar Ali Turabi MA, Pruthi N, Bhat D, Bhagavatula ID. Complex Chiari malformation: proposal of a new set of diagnostic criteria and outcomes after fusion surgery. World Neurosurg 2021;154:e677–e682
41. Behari S, Kalra SK, Kiran Kumar MV, Salunke P, Jaiswal AK, Jain VK. Chiari I malformation associated with atlanto-axial dislocation: focussing on the anterior cervico-medullary compression. Acta Neurochir (Wien) 2007;149(1):41–50, discussion 50
42. Salunke P, Karthigeyan M, Malik P, Panchal C. Changing perception but unaltered reality: how effective is C1-C2 fixation for Chiari malformations without instability? World Neurosurg 2020;136: e234–e244
43. Anderson PA, Oza AL, Puschak TJ, Sasso R. Biomechanics of occipitocervical fixation. Spine 2006;31(7):755–761
44. Kalra SK, Jain VK, Jaiswal AK, Behari S. Occipitocervical contoured rod stabilization: does it still have a role amidst the modern stabilization techniques? Neurol India 2007;55(4):363–368
45. Sardhara J, Behari S, Mohan BM, et al. Risk stratification of vertebral artery vulnerability during surgery for congenital atlanto-axial dislocation with or without an occipitalized atlas. Neurol India 2015;63(3):382–391
46. Furtado SV, Thakar S, Hegde AS. Correlation of functional outcome and natural history with clinicoradiological factors in surgically managed

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pediatric Chiari I malformation. Neurosurgery 2011;68(2):319–327, discussion 328
47. Hida K, Iwasaki Y. Syringosubarachnoid shunt for syringomyelia associated with Chiari I malformation. Neurosurg Focus 2001;11(1):E7
48. Klekamp J. Neurological deterioration after foramen magnum decompression for Chiari malformation type I: old or new pathology? J Neurosurg Pediatr. 2012 Dec;10(6):538–47
49. Soleman J, Roth J, Bartoli A, Rosenthal D, Korn A, Constantini S. Syringo-subarachnoid shunt for the treatment of persistent syringomyelia following decompression for Chiari type I malformation: surgical results. World Neurosurg 2017;108:836–843

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20 Nerve Transfers in Spinal Cord Injuries

Ketan Desai, Alay Khandhar, Pooja Salunkhe, Subhashree Hari, and Anushtup Raval

Introduction

Cervical spinal cord injury (SCI) causes devastating loss of upper-extremity and bladder–bowel functions and consequently, it takes away the independence of the patient. In such a situation, nerve transfer procedures are promising treatment options to reanimate and gain a part of upper limb function. SCI leads to chronic impairment and disability.[1] The incidence of SCI in India is 15 per million, with around 12,000 new cases of traumatic paraplegia and tetraplegia occurring each year. ResearchGate estimates that around 1.5 million people in India currently live with SCI and that 20,000 new cases are added each year with 50% of reported cases having cervical SCI causing tetraplegia.[1,2] Patients with SCI are mostly males in the age group of 16 to 30 years signifying higher incidence in the society's young, active, productive population.[3–6] SCI is a life-threatening condition that can lead to high rates of morbidity and mortality.[1]

The common causes of SCI are road accidents and falls. In India, fall from height rates are the highest among the etiological factors causing SCI. There is a gradual trend toward increased incidence of road traffic accidents indicating gradual urbanization of society and an increase in several vehicles on roads in India.[6] The incidence of secondary medical problems in the SCI population is high compared to the Western world. There is a lack of basic infrastructure and trained medical personnel, especially in rural areas, involved in the initial management of patients with SCI. A vast majority of people lack basic knowledge about the initial immobilization and transportation of these patients to higher centers. By the time the patient reaches a general or institutional hospital, there may be extensive damage to the spinal cord, which could have been prevented.[3]

The incidence of cervical SCI is greater than 50% among the SCI.[2] The resultant tetraplegia causes sensory–motor paralysis in the trunk and upper and lower extremities along with sphincter dysfunction. The recovery from a complete SCI is exceedingly rare and the affected individuals are left with permanent health loss and disability.[3,6] Patients with tetraplegia are dependent on residual motor function and the assistance of caregivers for mobility and activities of daily living.[7,8] Regaining arm and hand function is consistently rated as the highest functional priority for recovery above bowel and bladder function, sexual function, and pain control.[7] Current restoration strategies rely on maximizing and optimally redistributing residual muscle functions that remain under volitional control. Thus, targeted interventions that provide even incremental improvements in upper-extremity strength can have a significant impact on independence and quality of life.[9] The polio epidemic and World Wars led to the development and refinement of tendon transfers, which have long been the standard reconstructive approach for the upper extremity following SCI.[10] However, the past few decades have seen the emergence of nerve transfers from a salvage procedure for the management of peripheral nerve injuries to a powerful reconstructive tool for patients with SCI.[9,11–19] Patients with tetraplegia depend on residual upper-extremity function for mobility

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and activities of daily living, and small gain or partial recovery of upper-extremity functions can positively impact the quality of life.[9] Although a significant amount of work is devoted to investigating neuroprotective and neuroregenerative strategies after SCI, therapeutic interventions that provide a consistent and meaningful improvement in functional or strength outcomes after injury are lacking. The nerve transfers are a viable treatment option, used alone or combined with muscle and tendon transfers, to restore upper-extremity functions.[9] Using the same principles successfully applied for peripheral nerve and brachial plexus injuries, nerve transfers in SCI place regenerating axons that remain under volitional control close to the target motor end plates.[20] Nerve transfers use motor axons above the SCI to reinnervate target muscle groups below the SCI while preserving the original muscle natural biomechanics, force, and excursion.[20,21] In SCI, nerve transfer bypasses the damaged spinal cord area to deliver signal from the brain to the disconnected muscle following that injury. Using nerve transfers to restore hand and upper-extremity function is an exciting development in the surgical management of cervical SCI.[22] The nerve transfer procedures have been successful in peripheral nerve and brachial plexus injury, and the natural tendency is to assume that nerve transfer procedures have similar outcomes in SCI.[20] However, SCI patients present unique challenges and rigorous assessment of this new application of nerve transfer surgery is necessary before this approach can be applied widely to this unique and complex patient population.[21]

Since the late 1800s, there has been a huge development and refinement of tendon transfers, which became the primary surgical intervention to provide functional recovery in the upper extremity. In a tendon transfer procedure, a muscle, which is still well controlled but not critical for function, is repositioned so that it can perform the function of the muscle that no longer works. Tendon transfers have been the mainstay of reconstructive strategies for upper-extremity function in tetraplegia.[23] Tendon transfers are not time-sensitive and can be performed years following injury. In addition, the recovery concerning muscle strength is early when compared with nerve transfer procedures. However, they require extended postoperative immobilization, during which functional dependence is increased and a higher level of supportive care is required. Moreover, transfers may be complicated by tendon rupture, tenodesis failure, and/or loss of strength due to progressive stretching and altered biomechanics.[22–24]

The nerve transfer procedures employ a similar concept to that of tendon transfers. Instead of contracting a muscle, a nerve that has retained volitional control is cut and sutured to a nerve that has lost control due to injury.[25] The axons sprout from the donor nerve which grow and reinnervate the paralyzed muscle, restoring its control. In this way, the paralyzed muscle is activated to perform its original function. Over time, with rehabilitation and brain plasticity, the muscle strength of the reinnervated muscle increases.[25–28] However, the timing of the nerve transfer procedure following trauma or SCI is critical as delay can result in the progression of denervation within the affected nerve. The literature review has documented nerve transfer procedures being performed up to 2 to 3 years following SCI.[29]

SCI Pathophysiology and Its Implications in Nerve Transfers

In an injured spinal cord, there are three segments (**Fig. 20.1**):

- The region of the cord that is subjected to the injury—the injured metamere (IM).

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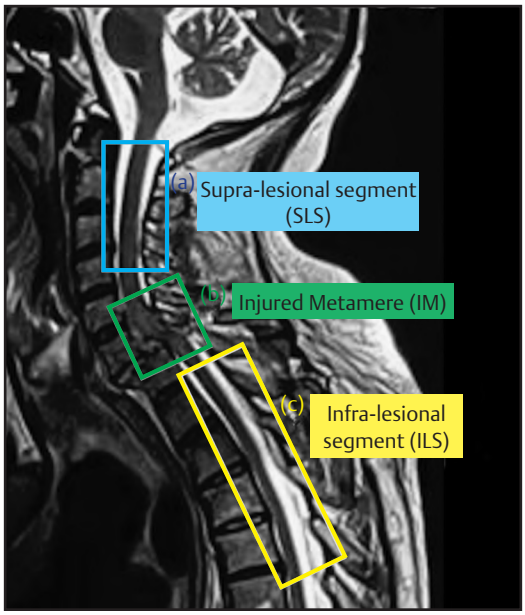

Fig. 20.1 Zones of spinal cord injury. Sagittal T2-weighted MRI image of cervical spine with complete spinal cord injury at C6–C7 level. **(a)** The supralesional segment (SLS; blue). **(b)** The injured metamere (IM; green): Zone of spinal cord injury. **(c)** The infralesional segment (ILS; yellow): Zone below the level of spinal cord injury.

- The normal region rostral to the IM—the supralesional segment (SLS).
- The region inferior to the IM—the infralesional segment (ILS).

The IM is the site of direct cord injury and it typically includes the destruction of the anterior horn cells and the axons that connect the cord to the central and peripheral nervous system (**Fig. 20.2**). There is resultant deinnervation of the target muscle with atrophy, fatty degeneration, and eventual loss of muscle integrity of those muscles that were the target of that spinal motor neuron. The nerve transfer procedure in this lesion should be performed within a year to salvage the distal target muscle. The ILS loses volitional control via disconnection from the upper motor neurons (UMNs). In contrast, the spinal lower motor neurons (LMNs) within this segment continue to innervate the target muscle, thereby maintaining the muscle's integrity and potential for recovery even years later. The nerves originating from the SLS can be transferred to the axon-depleted nerves of the IM region during the window of opportunity to recover these targets.[14,21,30–38]

Evolution of Nerve Transfers for Spinal Cord Injury

Nerve transfers are a peripheral nerve procedure with a significant clinical impact when applied in patients with SCI. Its application in peripheral nerves and brachial plexus has been well documented over the last many decades. The use of nerve transfer procedures in SCI is a more recent translation with a resurgence in its popularity. Unlike nerve transfers for upper-trunk brachial plexus injuries, which prioritize proximal arm functions such as elbow flexion and shoulder abduction, transfers for SCI aim to restore distal upper-extremity functions, including elbow extension, palmar grasp, key pinch, and release.[20]

The first clinical report of nerve transfer was reported in 1903 by Charles Balance who co-opted the spinal accessory nerve to the facial nerve for alleviation of facial nerve palsy. He found that facial movement was associated with shoulder-shrugging movement.[39] In 1913, Howard Tuttle was the first to report nerve transfer for brachial plexus repair.[40] Alexander Lurje in 1948 reported the use of various donors like the phrenic nerve and long thoracic nerve to re-innervate the musculocutaneous nerve for biceps flexion following C5–C6 nerve root injuries.[41] The nerve transfer procedures till 20 years back were considered salvage procedures when direct nerve grafting failed or was not available for repair. The pioneering work by Christophe Oberlin and Leechavengvongs Somsak in the 1990s, and Socolovsky's work on cerebral plasticity following nerve transfers led to a

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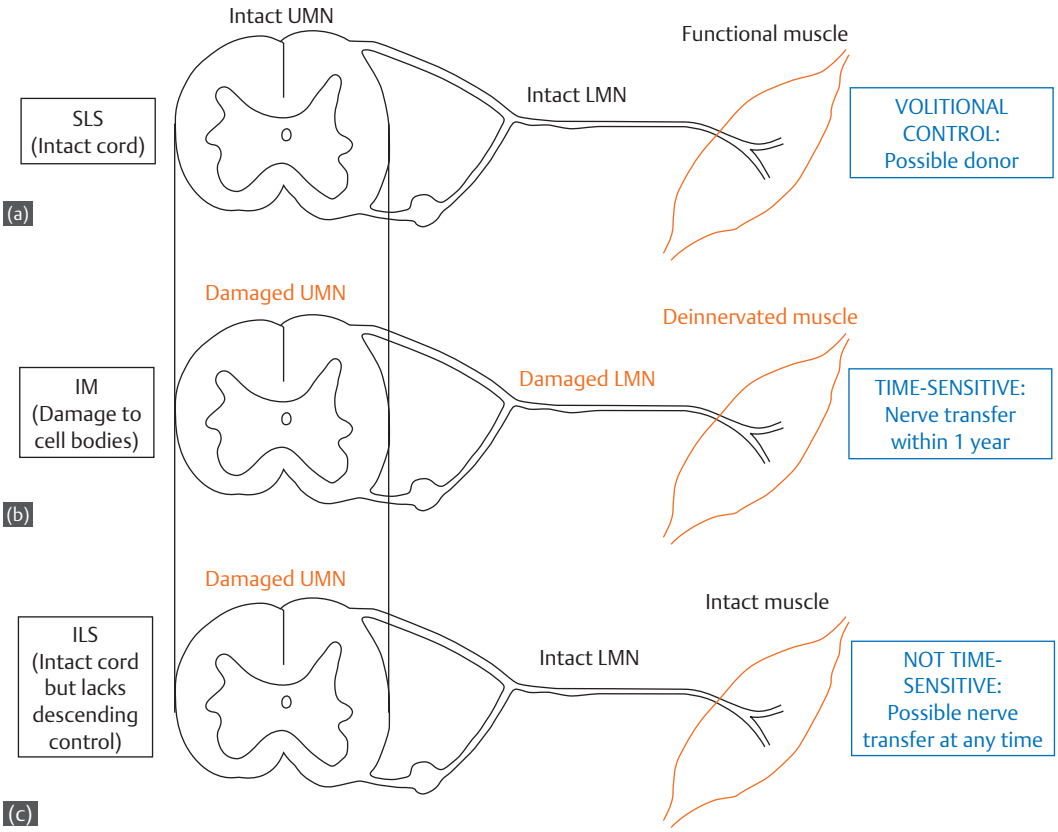

Fig. 20.2 Schematic representation of zones of injury. (a) Supralesional segment (SLS)—the upper motor neurons (UMNs), lower motor neurons (LMNs), and the corresponding muscle group are intact; so the volitional control is preserved; potential donors are found at this level. **(b)** Injured metamere (IM)—there is direct damage to the LMN, causing deinnervation of these potential recipient muscles. **(c)** Infralesional segment (ILS)—there is loss of UMN input, but the intact LMNs within this segment continue to innervate the corresponding muscle group.

surge in popularity with a high success rate without appreciable loss in the donor nerve function.[42,43] The nerve transfers became a viable option, and the results were comparable or even superior to nerve grafting procedures.

In patients with tetraplegia following SCI, restoration of hand function with elbow extension is the highest priority and even partial gain in arm and hand control can have a profound effect on functional independence and quality of life.[9]

Timing of Surgery and Preoperative Considerations

Nerve transfers should be performed after the reinnervation window to allow adequate waiting time and ensure optimal spontaneous recovery for lesional level myotomes. Bertelli et al recommended waiting for at least 6 months.[37] Although recovery of SCI may occur 2 years after injury, most of the recovery occurs in the first 6 months.[44] Muscles that

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remain paralyzed 6 months after the injury are not likely to recover or do not attain significant functional recovery.[45]

The extent of LMN injury at the injured segment must be adequately assessed particularly when the nerve transfer is contemplated at a point in time when the reinnervation window has elapsed. The nerve transfer procedure in a chronically denervated muscle should be avoided as the outcome is poor. A detailed clinical assessment is important with an examination of key muscle groups to determine the type of motor neuron injury (upper or lower motor neuron) by evaluating its power, tone, trophic status, relevant deep tendon reflex and range of motion of the joints, and limb deformity.[33] In addition, electrodiagnostic studies (electromyography and nerve conduction study) are beneficial to determine the extent of SCI. The presence of large number of fibrillations and positive sharp waves indicates chronically denervated muscle. The reduction of compound muscle action potential (CMAP) amplitude indicates axon or motor neuron loss.[32,33] Following a complete evaluation, the muscles are charted as: (1) functional muscles (innervated by SLS); (2) paralyzed and deinnervated muscles (innervated by injured metamere, with damage to LMN); and (3) paralyzed but innervated muscles (innervated by ILS, with preserved LMN). The boundaries between these three zones are not always clear-cut but often present with transition zones of muscles that are partially deinnervated.[21,33]

Restoration of Grip and Finger Flexion

For the reinnervation of hand and finger flexors, transfer of the brachialis branch of the musculocutaneous nerve to the anterior interosseous nerve (AIN) and median nerve motor branches is the most commonly reported strategy. The earliest report utilizing nerve transfer for SCI was by French surgeon Jean Benassy in 1966.[46] He anastomosed the distal musculocutaneous nerve after its branch from the biceps to the median nerve for regaining hand function in tetraplegic patients. The results were poor as the repair was far from the target muscle and the recipient median nerve was a mixed sensory-motor nerve. In 1991, Krasuski and Kiwerski anastomosed the brachialis branch and lateral antebrachial cutaneous nerve of the musculocutaneous nerve to the whole median nerve. They had good outcomes following the surgery, had good recovery of simple finger flexion, and useful grip in 32 out of 42 patients (76%) with significant qualitative improvements in ability and function. They also noted that young patients (<25 years) who underwent early surgery following SCI (within 3 months) derived greater benefit from the intervention.[47-49]

The more selective option of transfer of the brachialis branch of the musculocutaneous nerve to the AIN fascicle or specific muscle branches of the median nerve to reinnervate the flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), flexor pollicis longus (FPL), and flexor carpi radialis (FCR) is used[14,17,30,50-56] (**Fig. 20.3a**). Using this strategy, encouraging results were documented and the strength gained is helpful in finger flexion, with Medical Research Council (MRC) grade 3/5 in fingers and thumb flexion strength. The follow-up duration in the long term is about at least 12 to 18 months. With the brachialis to AIN transfer strategy, axonal regeneration occurs across relatively long distances (>15 cm), from the nerve coaptation site in the midarm to distal AIN and median nerve motor targets in the forearm, and therefore extended follow-up durations (>12 months) would be required to detect reinnervation attributable to the transfer.

Bertelli et al reported excellent results from single nerve transfers of the brachialis, brachioradialis, or extensor carpi radialis brevis (ECRB) branches to the AIN. They

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advocated proximal retrograde dissection of the AIN from the antecubital fossa to the midarm level.[57,58]

Reconstruction of Wrist, Thumb, and Finger Extension

The use of supinator muscle branches anastomosis to the posterior interosseous nerve (PIN), a branch of radial nerve, helps to gain wrist, thumb, and finger extension to gain the strength of extensor digitorum communis (EDC) and extensor pollicis longus and brevis (EPL/EPB) muscles (**Fig. 20.3b**). The outcome largely depends on the patient's age and the duration from the time of injury. In case reports and series reported in the literature, 60 to 100% of treated upper limbs achieved a good outcome (MRC grade ≥3/5) after an average of 6 to 24 months of follow-up.[9,14,17,19,51,55,56,59,60]

Reconstruction of Elbow Extension

In SCI, the axillary nerve branch may be used to reinnervate the triceps branches of the radial nerve to restore elbow extension and stability.[9,14,17,19,30,37,55,56] Bertelli and Ghizoni used the posterior division of the axillary nerve to anastomose with the long head of the triceps branch of the radial nerve to gain triceps function of elbow extension[19] (**Fig. 20.3c**). The other option for high cervical SCI is spinal accessory nerve to nerve to long head of triceps transfer using cable nerve graft (**Fig. 20.3d**). There was excellent long-term recovery to MRC grade ≥3/5 noted with this nerve transfer procedure for elbow extension. Isolated teres minor motor branches of the posterior division of the axillary nerve have also been used as donors for triceps muscle reinnervation transfers. This strategy notably leaves the posterior deltoid muscle intact if a muscle/tendon transfer is later considered to augment partial recovery or failure.[17,37]

Restoration of Shoulder Function and Stability

In high cervical SCI, spinal accessory branch to trapezius muscle is used to reinnervate the suprascapular nerve for gaining shoulder abduction and stability. The long-term results are excellent. This transfer is routinely used for regaining shoulder abduction function in patients with brachial plexus injury.[61]

Qualitative Improvements and Donor Site Morbidity

Patients with tetraplegia who underwent nerve transfer to recover upper-extremity function report significant quality-of-life improvements, with a renewed ability to perform activities of daily living, including self-catheterization, transfers, dressing, writing, and feeding. In addition, patients generally experienced minimal to no discernible donor-related weakness after surgery. Even in cases where donor muscle strength was downgraded, it was noted to be temporary and recovered over time.[61]

Rehabilitation

Effective rehabilitation is critical to achieve optimal functional recovery. Nerve transfers require focused re-learning of specific motor behavior to first strengthen the new connection.[62] Rehabilitation for nerve transfers in SCI is a developing field, but is generally approached in the following stages:

- **Preoperative stage**: Preoperatively, it is critical that the patient fully understands that the benefits of surgery will take time and require significant participatory effort to optimize functional restoration.
- **Acute postoperative phase**: The affected joints are partially immobilized for a few weeks following surgery to protect

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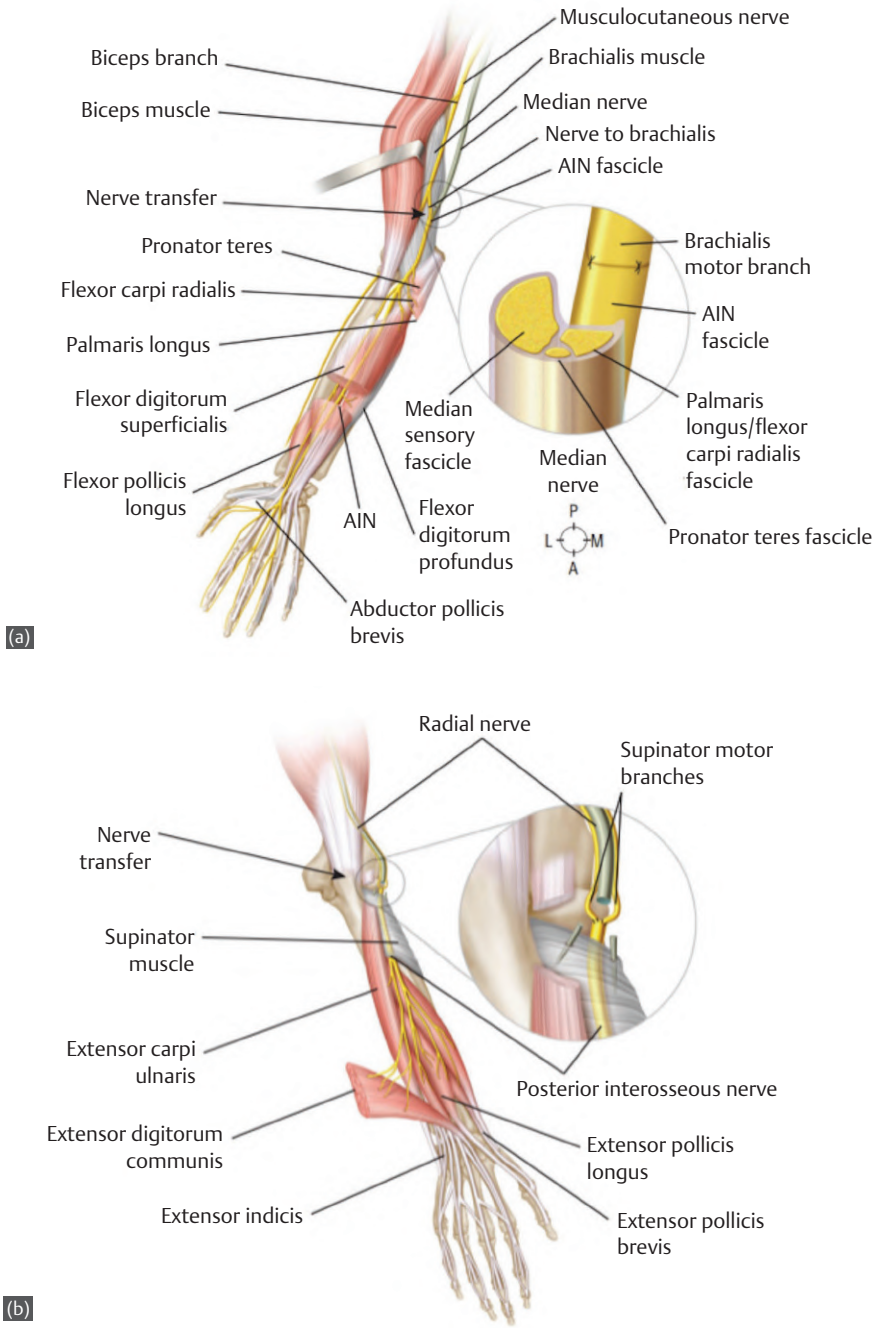

Fig. 20.3 Examples of nerve transfer procedures for spinal cord injury (SCI). (a) Brachialis branch of musculocutaneous nerve anastomosed with anterior interosseous nerve fascicle of median nerve to restore hand grasp and pinch. **(b)** Supinator branches of radial nerve anastomosed with posterior interosseous nerve to restore hand opening and release. *(Continued)*

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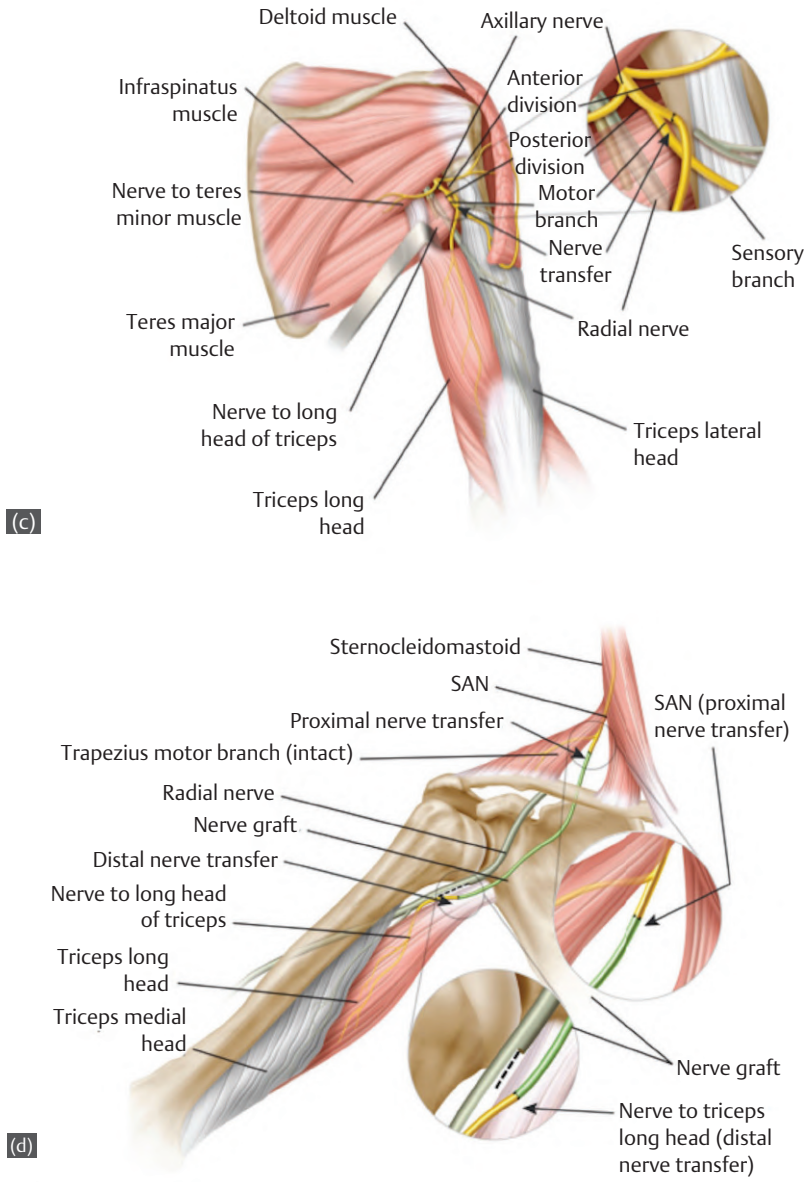

Fig. 20.3 *(Continued)* **(c)** Posterior division of axillary nerve anastomosed with radial nerve branch to long head of triceps to restore elbow extension. **(d)** Spinal accessory nerve branch anastomosed with radial nerve branch to long head of triceps muscle using cable nerve graft to restore elbow extension. (Image reproduced with permission from Javeed et al.[50] https://creativecommons.org/licenses/by/4.0/)

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the coaptation site and ensure proper wound healing. The patient should then return to a preoperative state following the initial healing process.

- **Rehabilitation phase**: There is intense therapy to maintain a passive range of motion (ROM) and educate the brain to incorporate the new function. Repetition and motor imagery, that is, thinking about performing the intended learned motor action, are proven techniques utilized to reinforce the new behavior.[63] This can be facilitated by mirror movements in the opposite arm in brachial plexus injuries but is not available in typical SCI. There is laboratory evidence that electrical stimulation enhances axon regeneration, but clinical improvement remains to be validated.

Nerve Transfer for Lower Limbs in SCI

The nerve transfer procedure in SCI affecting the cervical and dorsal spinal cord is challenging. In the lower extremity, unlike the upper extremity, the availability of donor nerves is limited and in addition, the regeneration distance is long. The two primary goals to be considered in the patient are ambulation and bowel–bladder control. The bowel–bladder function is considered a high priority by the patients. Similarly, the function required to create an effective transfer in the legs must be significantly stronger than that required by the upper extremity.

In dorsal SCI, attempts have been made to recruit more axon-rich upper-extremity sources for completely paralyzed lower extremities. The use of pedicled ulnar nerve tunneled down the chest wall to reinnervate proximal leg muscles has been reported with some degree of success.[64,65] However, with limited lower limb movement, compromising hand function is debatable. The nerve transfer procedure using intercostal nerves to the lumbar nerve roots demonstrated some degree of lower limb function enabling the patient to walk with ambulatory assistive devices.[66,67]

Patients with SCI consistently rate bladder function above lower limb recovery. Numerous nerve transfer procedures are suggested for achieving urinary bladder control with limited success as bladder control is a complex mechanism and autonomic reflexes play a dominant role. SCI often results in spastic detrusor activity or a dyssynergy between the detrusor and external sphincter. The use of functional electrical stimulation (FES) for bladder control has been employed since the late 1970s when Brindley achieved voiding in SCI patients following sacral anterior root stimulation (SARS) and is currently clinically approved as the VOCARE Bladder System.[68,69] This implantable, wireless SARS system is used to contract the detrusor muscle to void. However, electrical stimulation is nonspecific and stimulates the external sphincter also to contract, creating a dyssynergistic void.[68]

Nerve Transfer in Children with SCI

The treatment protocol in children with SCI remains the same as adults. Children unlike adults over time have recovery in the limbs function. Children with SCI live longer with the disability than adults. Hence, children with tetraplegia must be treated to improve their hand and upper-extremity function. In addition, SCI has a significant effect on the psychological development of children and its consequence on rehabilitation compliance. The caregivers, mainly the parents, play an important role in their rehabilitation process.[70]

Conclusion

Nerve transfer is a viable option for the restoration of critical upper limb function in SCI, which potentially improves the independence of the patient. Although the use of this technique for SCI is still in its infancy, it

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offers several advantages over the traditionally used tendon transfer procedure. The nerve transfer procedure is a relatively simple technique and does not require prolonged immobilization. In addition, it provides greater functional gain with the reconstruction of several upper limb functions in a single stage. The use of nerve transfers for motor control of locomotion in paraplegics remains experimental. The merits of nerve transfer warrant further study to evaluate its value for SCI in humans.

References

1. Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. J Neurotrauma 2004;21(10):1355–1370
2. National Spinal Cord Injury Database. Spinal cord injury facts and figures at a glance. 2022. Accessed October 21, 2022
3. GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(1):56–87
4. National Spinal Cord Injury Statistical Center. Spinal cord injury (SCI) 2016 facts and figures at a glance. J Spinal Cord Med 2016;39(4):493–494
5. Singh A, Tetreault L, Kalsi-Ryan S, Nouri A, Fehlings MG. Global prevalence and incidence of traumatic spinal cord injury. Clin Epidemiol 2014;6:309–331
6. World Health Organization -International Spinal Cord Society. International perspectives on spinal cord injury. World Health Organization. Accessed May 7, 2019
7. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 2004;21(10):1371–1383
8. Snoek GJ, IJzerman MJ, Hermens HJ, Maxwell D, Biering-Sorensen F. Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. Spinal Cord 2004;42(9):526–532
9. Bertelli JA, Ghizoni MF. Nerve transfers for elbow and finger extension reconstruction in midcervical spinal cord injuries. J Neurosurg 2015;122(1):121–127
10. Vastamäki M. Short-term versus long-term comparative results after reconstructive upper-limb surgery in tetraplegic patients. J Hand Surg Am 2006;31(9):1490–1494
11. Sinnott KA, Dunn JA, Wangdell J, Johanson ME, Hall AS, Post MW. Measurement of outcomes of upper limb reconstructive surgery for tetraplegia. Arch Phys Med Rehabil 2016;97(6, Suppl):S169–S181
12. Fox IK. Nerve transfers in tetraplegia. Hand Clin 2016;32(2):227–242
13. Bertelli JA, Ghizoni MF. Nerve transfers for restoration of finger flexion in patients with tetraplegia. J Neurosurg Spine 2017;26(1):55–61
14. Fox IK, Davidge KM, Novak CB, et al. Nerve transfers to restore upper extremity function in cervical spinal cord injury: update and preliminary outcomes. Plast Reconstr Surg 2015;136(4):780–792
15. Fox IK, Davidge KM, Novak CB, et al. Use of peripheral nerve transfers in tetraplegia: evaluation of feasibility and morbidity. Hand (N Y) 2015;10(1):60–67
16. Cain SA, Gohritz A, Fridén J, van Zyl N. Review of upper extremity nerve transfer in cervical spinal cord injury. J Brachial Plex Peripher Nerve Inj 2015;10(1):e34–e42
17. van Zyl N, Hahn JB, Cooper CA, Weymouth MD, Flood SJ, Galea MP. Upper limb reinnervation in C6 tetraplegia using a triple nerve transfer: case report. J Hand Surg Am 2014;39(9):1779–1783
18. Fridén J, Gohritz A. Muscle and nerve transfer in tetraplegia. J Neurosurg 2013;118(3):706–707
19. Bertelli JA, Ghizoni MF. Single-stage surgery combining nerve and tendon transfers for bilateral upper limb reconstruction in a tetraplegic patient: case report. J Hand Surg Am 2013;38(7):1366–1369
20. Ray WZ, Chang J, Hawasli A, Wilson TJ, Yang L. Motor nerve transfers: a comprehensive review. Neurosurgery 2016;78(1):1–26
21. Senjaya F, Midha R. Nerve transfer strategies for spinal cord injury. World Neurosurg 2013;80(6):e319–e326
22. Dunn JA, Sinnott KA, Rothwell AG, Mohammed KD, Simcock JW. Tendon transfer surgery for people with tetraplegia: an overview. Arch Phys Med Rehabil 2016;97(6, Suppl):S75–S80
23. Bednar MS. Tendon transfers for tetraplegia. Hand Clin 2016;32(3):389–396
24. Fridén J, Gohritz A. Tetraplegia management update. J Hand Surg Am 2015;40(12):2489–2500

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25. Hill EJR, Fox IK. Current best peripheral nerve transfers for spinal cord injury. Plast Reconstr Surg 2019;143(1):184e–198e
26. Gordon T, Yang JF, Ayer K, Stein RB, Tyreman N. Recovery potential of muscle after partial denervation: a comparison between rats and humans. Brain Res Bull 1993;30(3-4):477–482
27. Anastakis DJ, Malessy MJ, Chen R, Davis KD, Mikulis D. Cortical plasticity following nerve transfer in the upper extremity. Hand Clin 2008; 24(4):425–444, vi–vii
28. van Zyl N, Hill B, Cooper C, Hahn J, Galea MP. Expanding traditional tendon-based techniques with nerve transfers for the restoration of upper limb function in tetraplegia: a prospective case series. Lancet 2019;394(10198):565–575
29. Fox IK, Miller AK, Curtin CM. Nerve and tendon transfer surgery in cervical spinal cord injury: individualized choices to optimize function. Top Spinal Cord Inj Rehabil 2018;24(3):275–287
30. Brown JM. Nerve transfers in tetraplegia I: background and technique. Surg Neurol Int 2011; 2:121
31. Brown JM. The reconstructive neurosurgery of spinal cord injury. In: Dimitrijevic MR, Kakulas BA, McKay WB, Vrbova G, eds. Restorative Neurology of Spinal Cord Injury. New York: Oxford University Press; 2012:134–168
32. Brown JM, Vivio N, Sheean GL. The clinical practice of reconstructive neurosurgery. Clin Neurol Neurosurg 2012;114(5):506–514
33. Coulet B, Allieu Y, Chammas M. Injured metamere and functional surgery of the tetraplegic upper limb. Hand Clin 2002;18(3):399–412, vi
34. Fox IK, Mackinnon SE. Adult peripheral nerve disorders: nerve entrapment, repair, transfer, and brachial plexus disorders. Plast Reconstr Surg 2011;127(5):105e–118e
35. Davidge KM, Kahn LC, Novak CB, Juknis N, Ruvinskaya R, Fox IK. Restoring prehension/ wrist flexion and decreasing spasticity 11 years following spinal cord injury: a case study of use of the brachialis nerve transfer. Paper presented at: 2014 American Association of Hand Surgery Annual Meeting; Kauai, Hawaii; January 8–11, 2014
36. Fox IK, Novak CB, Krauss EM, et al. The use of nerve transfers to restore upper extremity function in cervical spinal cord injury. PM R 2018; 10(11):1173–1184.e2
37. Bertelli JA, Ghizoni MF, Tacca CP. Transfer of the teres minor motor branch for triceps reinnervation in tetraplegia. J Neurosurg 2011;114(5):1457–1460
38. Bertelli JA, Tacca CP, Winkelmann Duarte EC, Ghizoni MF, Duarte H. Transfer of axillary nerve branches to reconstruct elbow extension in tetraplegics: a laboratory investigation of surgical feasibility. Microsurgery 2011;31(5):376–381
39. Ballance CA, Ballance HA, Stewart P. Remarks on the operative treatment of chronic facial palsy of peripheral origin. BMJ 1903;1(2209):1009–1013
40. Tuttle H. Exposure of the brachial plexus with nerve transplantation. JAMA 1913;61(1):15–17
41. Lurje AS. On the use of N. musculocutaneous for neurotization of N. radialis in cases of very large defects of the latter. Ann Surg 1948;128(1):110–115
42. Oberlin C, Béal D, Leechavengvongs S, Salon A, Dauge MC, Sarcy JJ. Nerve transfer to biceps muscle using a part of ulnar nerve for C5-C6 avulsion of the brachial plexus: anatomical study and report of four cases. J Hand Surg Am 1994;19(2):232–237
43. Socolovsky M, Malessy M. Brain changes after peripheral nerve repair: limitations of neuroplasticity. J Neurosurg Sci 2021;65(4):421–430
44. Waters RL, Sie IH, Gellman H, Tognella M. Functional hand surgery following tetraplegia. Arch Phys Med Rehabil 1996;77(1):86–94
45. Kozin SH. Tetraplegia. J Am Soc Surg Hand 2002;2(3):141–152
46. Benassy J. Transposition of the musculo-cutaneous nerve upon the median nerve. Case report. Med Serv J Can 1966;22(7):695–697
47. Kiwerski J. Recovery of simple hand function in tetraplegia patients following transfer of the musculo-cutaneous nerve into the median nerve. Paraplegia 1982;20(4):242–247
48. Kiwerski J. [Transplantation of the musculocutaneous nerve on the median nerve in an attempt at improving the function of the hand of a tetraplegic.] Pol Orthop Traumatol 1975;40:173–178 (Polish)
49. Krasuski M, Kiwerski J. An analysis of the results of transferring the musculocutaneous nerve onto the median nerve in tetraplegics. Arch Orthop Trauma Surg 1991;111(1):32–33
50. Javeed S, Dibble CF, Greenberg JK, et al. Upper limb nerve transfer surgery in patients with tetraplegia. JAMA Netw Open 2022;5(11):e2243890 https://creativecommons.org/licenses/by/4.0/
51. Emamhadi M, Andalib S. Double nerve transfer for restoration of hand grasp and release in C7

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tetraplegia following complete cervical spinal cord injury. Acta Neurochir (Wien) 2018;160(11): 2219–2224
52. Fox IK, Novak CB, Kahn LC, Mackinnon SE, Ruvinskaya R, Juknis N. Using nerve transfer to restore prehension and grasp 12 years following spinal cord injury: a case report. Spinal Cord Ser Cases 2018;4:37
53. Hawasli AH, Chang J, Reynolds MR, Ray WZ. Transfer of the brachialis to the anterior interosseous nerve as a treatment strategy for cervical spinal cord injury: technical note. Global Spine J 2015;5(2):110–117
54. Mackinnon SE, Yee A, Ray WZ. Nerve transfers for the restoration of hand function after spinal cord injury. J Neurosurg 2012;117(1):176–185
55. Sananpanich K, Kraisarin J, Siriwittayakorn W, Tongprasert S, Suwansirikul S. Double motor nerve transfer for all finger flexion in cervical spinal cord injury: an anatomical study and a clinical report. J Hand Surg Am 2018;43(10):920–926
56. Ward JA, Young K, Shirley C, Miller C, Tan S, Power D. Rewiring the arm: nerve transfer for restoration of upper limb function in traumatic cervical spinal cord injury. Trauma (United Kingdom) 2015;17(4):315
57. Bertelli JA, Mendes Lehm VL, Tacca CP, Winkelmann Duarte EC, Ghizoni MF, Duarte H. Transfer of the distal terminal motor branch of the extensor carpi radialis brevis to the nerve of the flexor pollicis longus: an anatomic study and clinical application in a tetraplegic patient. Neurosurgery 2012;70(4):1011–1016, discussion 1016
58. Fridén J, Reinholdt C, Turcsányii I, Gohritz A. A single-stage operation for reconstruction of hand flexion, extension, and intrinsic function in tetraplegia: the alphabet procedure. Tech Hand Up Extrem Surg 2011;15(4):230–235
59. Bertelli JA, Ghizoni MF. Nerve and free gracilis muscle transfers for thumb and finger extension reconstruction in long-standing tetraplegia. J Hand Surg Am 2016;41(11):e411–e416
60. Bertelli JA, Tacca CP, Ghizoni MF, Kechele PR, Santos MA. Transfer of supinator motor branches to the posterior interosseous nerve to reconstruct thumb and finger extension in tetraplegia: case report. J Hand Surg Am 2010;35(10):1647–1651
61. Bhatnagar A. Spinal accessory nerve transfer to the suprascapular nerve to restore shoulder function in brachial plexus injury: management nuances. Neurol India 2019;67(Suppl):S29–S31
62. Khalifeh JM, Dibble CF, Van Voorhis A, et al. Nerve transfers in the upper extremity following cervical spinal cord injury. Part 1: Systematic review of the literature. J Neurosurg Spine 2019;31(5):629–640
63. Socolovsky M, Malessy M. Brain changes after peripheral nerve repair: limitations of neuroplasticity. J Neurosurg Sci 2021;65(4):421–430
64. Patil A. Intercostal nerves to spinal nerve roots anastomosis (spinal cord bypass) and Harrington rod fusion in traumatic paraplegia—technical note. Acta Neurochir (Wien) 1981;57(3-4):299–303
65. Brunelli GA, Brunelli GR. Restoration of walking in paraplegia by transferring the ulnar nerve to the hip: a report on the first patient. Microsurgery 1999;19(5):223–226
66. Lim HH, Baskaran. Intercostal nerve neurotization of the femoral nerve in patients with paraplegia—an anatomical feasibility study. Med J Malaysia 2001;56(Suppl C):61–65
67. Zhang S, Johnston L, Zhang Z, et al. Restoration of stepping-forward and ambulatory function in patients with paraplegia: rerouting of vascularized intercostal nerves to lumbar nerve roots using selected interfascicular anastomosis. Surg Technol Int 2003;11:244–248
68. Martens FM, Heesakkers JP. Clinical results of a Brindley procedure: sacral anterior root stimulation in combination with a rhizotomy of the dorsal roots. Adv Urol 2011;2011:709708
69. Creasey GH, Grill JH, Korsten M, et al; Implanted Neuroprosthesis Research Group. An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: a multicenter trial. Arch Phys Med Rehabil 2001;82(11):1512–1519
70. Peljovich A, Gillespie B, Bryden AM, et al. Rehabilitation of the hand and upper extremity in tetraplegia. In: Skirven T, Osterman A, Fedorczyk J, et al, eds. Rehabilitation of the Hand and Upper Extremity. 6th ed. Philadelphia: Elsevier Mosby; 2011

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21 Protons Beam versus Conventional Radiation in Chordomas

Srinivas Chilukuri, Ramakrishna Kamath, and Rakesh Jalali

Introduction

Chordomas are relatively rare epithelial tumors that are also called as notochordal sarcomas, which constitute 1 to 4% of bone sarcomas.[1] They are usually characterized by relatively indolent growth like low-grade tumors but also often exhibit aggressive local tumor progression similar to malignant tumors. Incidence of chordomas has been reported to be 0.08/100,000 population with predominance among men with highest incidence in 5th to 6th decades.[1] Less than 5% of all chordomas are noted in children and adolescents.[1] One of the largest retrospective studies (400 patients) reported in 2001, with possibly longest reported follow-up, demonstrated 5-, 10-, and 20-year survival to be 67.6, 39.9, and 13.1% respectively.[2]

As a rule, these appear almost always in the midline with skull base (33%) being the most common location followed by mobile spine (32%) and sacrum (30%).[3] Histologically, they have been divided into classical chordomas, chondroid chordomas, and de-differentiated chordomas. These tumors are also characterized by expression of brachyury, which is a marker of undifferentiated embryonic notochord. This immunohistochemistry marker distinguishes it from chondrosarcomas and other chondroid tumors.

Surgery for Chordomas

The indolent nature of the disease and discontinuous spread along muscular planes destroying the bone/bony foramina along with impingement/destruction of the nerves makes managing these tumors extremely challenging. Although surgery is considered the usual standard of care, due to relatively large tumor volumes at diagnosis with ill-defined margins and involvement of critical neural structures, en-bloc resection is nearly impossible (except for lower sacral/coccygeal tumors) and even gross total resection is extremely challenging. In patients with sacral and mobile spinal tumors, Kaiser et al demonstrated that an en-bloc resection without violation of tumor intraoperatively more than doubled the local control compared to patients who had intraoperative tumor violation.[4] Similarly, Fuchs et al showed a significantly improved local control with radical resections (2.27 years) compared to subtotal resections (8 months).[5] Many other publications have corroborated this difference between gross total resections and subtotal resections, supporting aggressive radical surgeries (**Table 21.1**). In patients with tumors in the clivus and skull base, where en-bloc or even radical gross total resection is extremely challenging, total or near-total intralesional resection followed by radical dose of radiation therapy is considered appropriate.

In summary, the overarching philosophy in the management of chordoma specifically with respect to surgery is that an en-bloc resection/gross total resection should be performed where feasible and partial debulking (anything less than gross total resection) should only be performed if that is done to relieve neural

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Table 21.1 Summary of studies reporting outcomes of subtotal resection with or without adjuvant radiation therapy

	Number of patients	Location	Percentage receiving adjuvant RT	Follow-up (months)	5-year estimates (%)		10-year estimates (%)	
					OS	LRFS	OS	LRFS
Rachinger et al[6]	47	Skull base	64	62	83	NR	NR	NR
Ouyang et al[7]	77	Skull base	29	60	71	45	46 (8 years)	18 (8 years)
Di Maio et al[8]	95	Skull base	35	38	74	56	NR	NR
Yasuda et al[9]	40	Skull base	75	57	70	NR	NR	NR
Wang et al[10]	14	Skull base & cervical spine	100	59	86	50	NR	NR
Choi et al[11]	97	Skull base	100	50	55	NR	36	NR
Wu et al[12]	106	Skull base	38	64	68	47	60	12
Sen et al[13]	71	Skull base	62	66	75	NR	NR	NR

Abbreviations: LRFS, local recurrence-free survival; NR, not reported; OS, overall survival; RT, radiation therapy.

compression or severe symptoms associated with chordoma. Although neurological functional preservation should remain an important goal for surgeons even at the cost of postoperative residual tumor, indiscriminate use of subtotal resection leads to inferior long-term outcomes compared to those receiving aggressive radiation or particle beam therapy in the definitive setting.

Conventional Radiation Therapy for Chordomas

Since less than 50% of sacral chordomas and much lesser percentage in skull base and rest of the spinal chordomas undergo an en bloc resection, in most patients chordomas recur locally. Radiation therapy in the adjuvant setting is known to delay or prevent recurrence. There is a large body of evidence that the tumor control in patients with chordomas is directly proportional to the prescription doses with doses higher than 70 Gy[14] leading to 5-year local control of more than 65 to 70%. Largely with the use of conventional therapies, higher doses as described above are extremely challenging to deliver due to proximity of these tumors to radiosensitive critical serial organs such as brain stem (maximum dose tolerance of 63 Gy), spinal cord (maximum dose tolerance of 50–54 Gy), optic nerves, chiasm (maximum dose tolerance of 50–56 Gy), etc. Even with advanced photon techniques such as Intenisty-modulated radiation therapy (IMRT), Volumetric modulated arc therapy (VMAT), or helical tomotherapy, such doses are difficult to achieve uniformly within tumors. Most studies evaluating photon-based conformal radiation therapy approaches or stereotactic radiotherapy had small patient numbers, were retrospective studies with inherent biases, and had relatively short follow-up periods.[15] In a systematic review of studies published recently, Saito et al reported outcomes with various photon therapy techniques; the 5-year progression-free survival was only 40%.[15]

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Particle Therapy for Chordomas and Comparison with Conventional Radiation (Photons)

There is a worldwide consensus on use of particle beam therapy for patients of chordomas of any location. There are several reasons for this overwhelming consensus.

Particle therapy such as proton beam therapy (PBT), due to its physical characteristic of a Bragg peak (**Fig. 21.1**), can create a very sharp dose gradient, enabling delivery of very large prescription doses to the tumor while respecting the tolerance doses of all the important critical structures as described above. Apart from the physical advantage, PBT is known to have a higher biological effect due to a higher linear energy transfer (LET) of protons compared to X-rays. The higher LET protons contribute to higher biological effect, and although its relative biological effectiveness (RBE) is averaged 10% higher compared to photons/X-rays, it is known to vary between 10 and 50% higher (**Fig. 21.2**). Both these factors—physical and biological characteristics—make PBT far more attractive in chordomas at least theoretically. As with conventional radiation, PBT has witnessed remarkable improvements in its technology over the last three and half decades. The current standard of intensity modulated proton beam therapy (IMPT) with on-board image guidance, modern treatment/planning calculation algorithms such as Monte Carlo based algorithms, and advanced planning systems have resulted in quite remarkable results in these challenging tumors (**Fig. 21.3**). In a study by Torres et al, PBT plans satisfied the dose volume constraints better than IMRT plans (meaning closely achieving highest conformity to the tumors and lowest possible dose to the normal organs at risk).[16] In another study

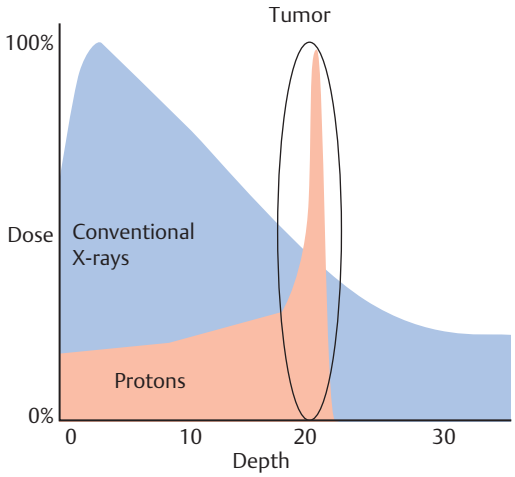
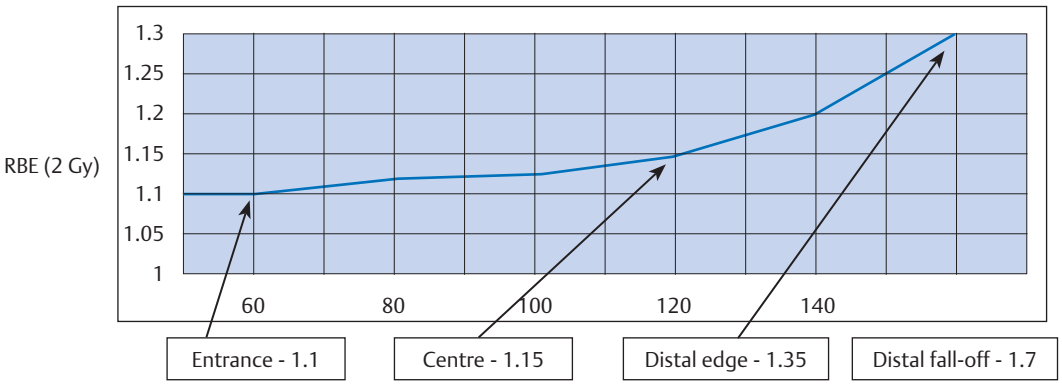


Fig. 21.1 Proton Bragg peak and comparison with X-rays/photons.



Values averaged over all cell lines and SOBPs for in-vitro cell survival

Fig. 21.2 Radiobiological effectiveness of proton beams with respect to location in the Bragg peak.

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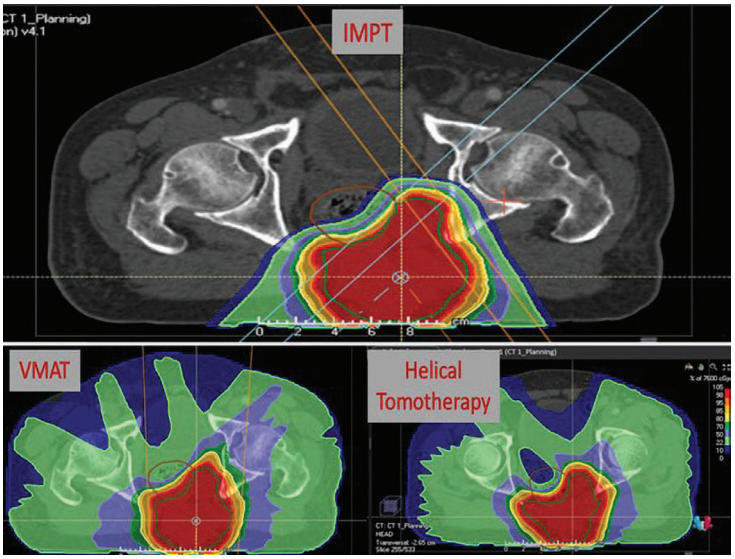

Fig. 21.3 Comparative dosimetric plan between intensity modulated proton beam therapy (IMPT) and volumetric modulated arc therapy (VMAT) and tomotherapy.

by Noufal et al, intensity modulated proton therapy plans were more robust compared to IMRT plans, with lesser worst case maximum doses to important serial neural structures such as spinal cord, brain stem, and optic apparatus.[17] Another advantage with PBT is lesser need for a dosimetric compromise. These compromises are more likely to be made with photon-based approaches due to less sharp dose gradients toward serial neural structures. In a study by Chilukuri et al, these dosimetric compromises have been shown to be associated with inferior 2-year local control.[18] To limit these dosimetric compromises that are sometimes made in patients with tumors that are closely abutting the neural structures, targeted fat spacer (patient's own fat) has been tried to create optimal separation between the tumor and the neural structure. The separation enables delivery of tumoricidal dose while respecting the tolerance of the normal structures (**Fig. 21.4**).

There are no prospective studies including randomized trials comparing proton and photon therapy. In a cohort of more than 151 skull base chordomas treated at PSI, Zurich, Weber et al demonstrated a 7-year local control of 71% and an overall survival of 72%.[19] They found that brain stem or optic apparatus compression by the tumor (due to which dose to a portion of the tumor may have been compromised) and residual gross tumor volume (GTV) >25 cc were associated with inferior local control and overall survival. Another study by Holtzman et al in a cohort of 112 patients with skull base chordomas showed 72% 5-year local control and 78% 5-year overall survival.[20] They also showed that with gross total resection the 5-year local control was 95% with no serious (grade ≥3) acute toxicities noted. Similarly, in a cohort of 51 patients with chordomas of mobile spine including sacrum, Indelicato et al demonstrated 4-year local control and overall survival of 58 and 72%, respectively. Important findings in the study were as follows: in patients with gross residual disease versus patients with only microscopic disease, there was no difference in local control; metal implants (in 53%) also did not alter outcomes; and patients treated upfront with PBT had a better local control and disease-free survival compared to patients who received PBT at the time of recurrence.[21] It is important to note

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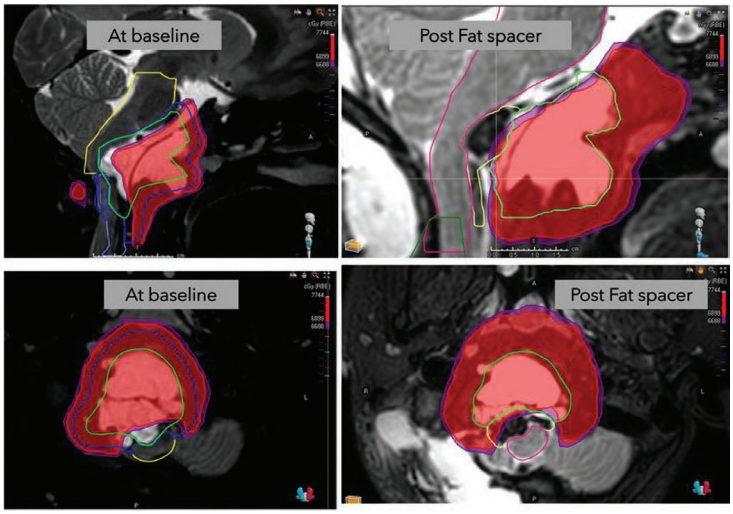

Fig. 21.4 Neural structure separation from the tumor with fat spacer.

that in the presence of metal implants, there can be a significant dosimetric uncertainty with PBT (which means that there could be discrepancy between delivered/absorbed doses compared to the doses calculated as per the treatment planning system). Traditionally, this uncertainty has led to inferior outcomes compared to those patients who did not have metal implants in close proximity to the tumor/tumor bed.[22] However, more modern algorithms (such as Monte Carlo algorithm) and uncertainty mitigation strategies (e.g., combining proton–photon based techniques) have resulted in more robust delivery of PBT, which has resulted in improved outcomes irrespective of metal implantation.

In a systematic review and meta-analysis published recently, Saito et al comparing outcomes of photons versus proton therapy for skull base chordomas showed that the 5-year progression-free survival was superior with PBT (68%) compared to photons (40%).[15] However, the rates of brain necrosis were higher with PBT and the authors recommended more careful planning to avoid this complication. In another large patient retrospective study of the National Cancer Database in the USA, Palm et al evaluated 715 chordomas of all locations and demonstrated that patients who received PBT had a higher 5-year overall survival compared to photon-based techniques.[23] They also demonstrated that higher doses were an important predictor of outcomes for both photons and PBT. Both the above-mentioned studies have several limitations. Although these results need to be cautiously interpreted due to the inherent limitations of these studies, the general direction of these results are consistent with the popular consensus that particle therapy is superior to photon-based techniques for all chordomas. Based on the above-discussed factor, most consensus-based guidelines such as ASTRO model policies,[24] European Particle Therapy Network,[25] and country-specific guidelines of UK, Netherlands, and others[25] now recommend PBT for chordomas of all locations in the definitive, postoperative, and in recurrent settings.

Response Assessment after Radiation/Proton Beam Therapy

Due to the relatively indolent nature of these tumors, the responses to the radiation or PBT is relatively slow and regression in the

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physical size of the tumor is extremely gradual with T50 of approximately 2.5 years (the time taken for the tumor to become half in size compared to the pre-treatment disease).[26] It is also important to note that standard imaging-based response criteria such as RECIST for solid tumors or modified Choi criteria for sarcomas may not be perfectly appropriate. Also, caution needs to be exercised in situations when there are metal implants near the residual irradiated tumors or tumor bed as they usually throw significant artefacts which may make accurate imaging interpretation very challenging despite the use of artefact reduction software. Lower Tesla imaging (1.5T or lesser) and two-dimensional sequences may be slightly better than 3T and three-dimensional imaging during MRI.

Conclusion

En-bloc resection or gross total resections which results in best possible outcomes in patients with chordomas is relatively rare and is extremely challenging due to the location of these tumors. Intralesional resections resulting in subtotal resections are often futile in controlling these tumors and should only be considered when there is neural structure compression or abutment or in the presence of considerable symptoms. PBT is preferable local therapy in the postoperative, definitive, and recurrent settings. PBT like conventional radiation therapy has been evolving and modern PBT seems to be significantly superior compared to modern photon techniques due to a sharper gradient of the physical doses along with higher biological effect. Modern PBT studies have shown a 5- to 7-year local control ranging from 60 to 70% for both skull base and mobile spinal/sacral chordomas.

References

1. Young VA, Curtis KM, Temple HT, Eismont FJ, DeLaney TF, Hornicek FJ. Characteristics and patterns of metastatic disease from chordoma. Sarcoma 2015;2015:517657
2. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. Cancer Causes Control 2001;12(1):1–11
3. Das P, Soni P, Jones J, et al. Descriptive epidemiology of chordomas in the United States. J Neurooncol 2020;148(1):173–178
4. Kaiser TE, Pritchard DJ, Unni KK. Clinicopathologic study of sacrococcygeal chordoma. Cancer 1984; 53(11):2574–2578
5. Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. J Bone Joint Surg Am 2005;87(10):2211–2216
6. Rachinger W, Eigenbrod S, Dützmann S, et al. Male sex as a risk factor for the clinical course of skull base chordomas. J Neurosurg 2014;120(6):1313–1320
7. Ouyang T, Zhang N, Zhang Y, et al. Clinical characteristics, immunohistochemistry, and outcomes of 77 patients with skull base chordomas. World Neurosurg 2014;81(5-6):790–797
8. Di Maio S, Rostomily R, Sekhar LN. Current surgical outcomes for cranial base chordomas: cohort study of 95 patients. Neurosurgery 2012;70(6):1355–1360, discussion 1360
9. Yasuda M, Bresson D, Chibbaro S, et al. Chordomas of the skull base and cervical spine: clinical outcomes associated with a multimodal surgical resection combined with proton-beam radiation in 40 patients. Neurosurg Rev 2012;35(2):171–182, discussion 182–183
10. Wang Y, Xiao J, Wu Z, et al. Primary chordomas of the cervical spine: a consecutive series of 14 surgically managed cases. J Neurosurg Spine 2012; 17(4):292–299
11. Choi D, Melcher R, Harms J, Crockard A. Outcome of 132 operations in 97 patients with chordomas of the craniocervical junction and upper cervical spine. Neurosurgery 2010;66(1):59–65, discussion 65
12. Wu Z, Zhang J, Zhang L, et al. Prognostic factors for long-term outcome of patients with surgical resection of skull base chordomas—106 cases review in one institution. Neurosurg Rev 2010; 33(4):451–456
13. Sen C, Triana AI, Berglind N, Godbold J, Shrivastava RK. Clival chordomas: clinical management, results, and complications in 71 patients. J Neurosurg 2010;113(5):1059–1071

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14. Banfield W, Ioakeim-Ioannidou M, Goldberg S, et al. Definitive high-dose, proton-based radiation for unresected mobile spine and sacral chordomas. Radiother Oncol 2022;171:139–145
15. Saito T, Mizumoto M, Oshiro Y, et al. Systematic review and meta-analysis of particle beam therapy versus photon radiotherapy for skull base chordoma: TRP-Chordoma 2024. Cancers (Basel) 2024;16(14):2569
16. Torres MA, Ballo MT, Butler CE, et al. Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. Int J Radiat Oncol Biol Phys 2007;67(4):1124–1129
17. Noufal MP, Widesott L, Sharma SD, Righetto R, Cianchetti M, Schwarz M. The role of plan robustness evaluation in comparing protons and photons plans—an application on IMPT and IMRT plans in skull base chordomas. J Med Phys 2020;45(4):206–214
18. Chilukuri S, Burela N, Sundar S, Kamath R, Nangia S, Arjunan M, Kumar R, Ramanujam V, Chacko A, Sharma DS, Jalali R. Impact of Dosimetric Compromises on Early Outcomes of Chordomas and Chondrosarcomas Treated With Image-guided Pencil Beam Scanning Proton Beam Therapy. Adv Radiat Oncol. 2024. 28;9(10):101582.
19. Weber DC, Malyapa R, Albertini F, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. Radiother Oncol 2016;120(1):169–174
20. Holtzman AL, Rotondo RL, Rutenberg MS, et al. Clinical outcomes following dose-escalated proton therapy for skull-base chordoma. Int J Part Ther 2021;8(1):179–188
21. Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. Int J Radiat Oncol Biol Phys 2016;95(1):297–303
22. Staab A, Rutz HP, Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. Int J Radiat Oncol Biol Phys 2011;81(4):e489–e496
23. Palm RF, Oliver DE, Yang GQ, Abuodeh Y, Naghavi AO, Johnstone PAS. The role of dose escalation and proton therapy in perioperative or definitive treatment of chondrosarcoma and chordoma: an analysis of the National Cancer Data Base. Cancer 2019;125(4):642–651
24. ASTRO Model Policies. Proton Beam Therapy (PBT). Accessed at: https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROPBTModelPolicy.pdf
25. Zientara N, Giles E, Le H, Short M. A scoping review of patient selection methods for proton therapy. J Med Radiat Sci 2022;69(1):108–121
26. Kim YJ, Cho KH, Lim YK, et al. The volumetric change and dose-response relationship following hypofractionated proton therapy for chordomas. Acta Oncol 2014;53(4):563–568

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22 Current Treatment Paradigms in Management of Cervical Disk Disease: ACDF versus Disk Replacement, the Controversies!

Sachin Anil Borkar, Kushagra Pandey, Akshay Ganeshkumar, P K Sahoo, and Shashank Sharad Kale

Introduction

Cervical disk disease is one of the most debilitating acquired conditions in patients older than 50 years of age, causing pain, neurological deficits, and reduced quality of life. It often becomes neurologically more compromising than its lumbar counterpart. Just like any other neurological condition, its treatment has undergone paradigm changes over time. This has led to controversies on various aspects on whether to approach the pathology via posterior approach or anterior and whether fusion or motion-preserving devices are necessary. Initially a posterior approach and decompression of neural structures was the preferred treatment approach for cervical degenerative disk disease. However, it got slowly replaced by anterior approaches and diskectomy with or without implantation of various spacers. The anterior cervical diskectomy with fusion (ACDF) slowly emerged as a gold standard technique; however, the fear of adjacent segment disease further shifted the gears toward motion-preserving surgeries and led to the popularity of cervical disk replacement (CDR). Both these procedures have been supplemented by various endoscopic or minimally invasive anterior or posterior cervical approaches. This chapter explores both these treatments in depth, examining their histories, methodologies, advantages, disadvantages, and clinical outcomes to guide treatment decisions.

History of Cervical Disk Disease

Andreas Vesalius (1514–1564), an anatomist and surgeon, was the first to describe the intervertebral disc in 1543. In 1928, Stookey reported on several syndromes caused due to cervical disk disease; however, he interpreted the prolapse as chordoma or tumors of the notochord.[1] It was not until 1934, when Mixter and Barr proposed the intervertebral disk theory and identified them as reasons of neck pain, radicular pain, and myelopathy.[2] In the past, posterior surgical approaches were the usual method used to treat cervical disk disease symptoms. In the latter half of the 20th century, it became evident that the primary issue with this method was the difficulty in identifying and excising compressive structures that are located in front of the spinal cord and nerve roots. An anterior surgical approach to the cervical spine was developed

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as a result of the requirement for improved access to reach anterior compressing elements. The 1950s saw the development of ACDF by Dr. Ralph Cloward.[3] This procedure, which involves removing the herniated disk and fusing the adjacent vertebrae, became a standard treatment for cervical disk disease. The 1960s and 1970s brought further refinements in surgical methods, including the use of microsurgical techniques to improve precision and outcomes. The late 20th century witnessed the rise of minimally invasive surgical techniques. These approaches aimed to reduce recovery times and complications associated with traditional open surgeries. Techniques such as microdiskectomy and the use of endoscopes allowed surgeons to perform precise operations with smaller incisions. In the early 21st century, CDR emerged as an alternative to fusion. This technique involves replacing the damaged disk with an artificial one, preserving more natural neck movement compared to fusion. The FDA approved the first CDR device in 2007, marking a new era in the treatment of cervical disk disease.

Pathophysiology of Cervical Disk Herniation

One can categorize the cervical spine into functional groups, with C1–C2 accounting for about 40% of axial rotation. The subaxial cervical spine bears the brunt of the remaining axial rotation, with the C4–C7 levels offering the greatest range of motion. Nearly 50% of neck flexion occurs at occiput–C2 region and remaining occurs at subaxial region. Disk degeneration, facet arthropathy, and pathologic alterations such as ossification or hypertrophy in the ligamentum flavum and posterior longitudinal ligament (PLL) are all part of the pathophysiology for disk herniation. A hydrated proteoglycan aggrecan-rich nucleus pulposus and an outer fibrous annulus fibrosus make up the cervical disk in young people. The lordotic alignment that is naturally present in a healthy cervical spine is crucial for load sharing. The force vector is distributed across the middle part of the spine due to cervical lordosis. Degenerative alterations associated with recurrent mechanical stresses are a result of aging and can be exacerbated by trauma. Over time proteoglycan loses hydration leading to loss of viscoelasticity of nucleus pulposus. This results in loss of disk height and volume, placing increased load on annulus fibrosus. Laxity in the ligaments and posterior zygapophyseal joints occurs as degeneration advances, resulting in spondylolisthesis and cervical curvature straightening. As a result, there is facet and ligamentous hypertrophy, and osteophyte development is brought about by biomechanical tension between neighboring end plates.[4] Because of the absence of lordosis, the force vector is moved anteriorly, adding more tension to the already damaged disk space.

Epidemiology of Cervical Spondylosis

The prevalence of cervical disk disease increases with age. Numerous radiographic investigations have examined the epidemiology of cervical spondylosis. One of the first studies, conducted by Lawrence in 1969, demonstrated that the prevalence, as determined by cervical plain radiographs, increases with age.[5] Spondylosis (grades 1 to 4) was more common in patients aged 34 to 65, rising from 15 to 60 to 90%. Moderate to severe cases of the disease, with grades 2 to 4, affected 8, 55, and 85% of patients, respectively. Boden and colleagues showed the prevalence of cervical degeneration signs in 90% of males more than 50 years of age and 90% females older than 60 years of age.[6] The risk factors for increased development of disk disease include smoking, obesity, trauma, high-impact sports, and even genetic predisposition.

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Clinical Features

Neck Pain

Pain can range from mild discomfort to severe, debilitating pain, often exacerbated by movement or certain positions. It may be localized to the neck or radiate to the shoulders, arms, and hands. It has a significant myofascial component, and the prevalence can be around 14 to 15%.[7] Disk degeneration and cervical facet joints both contribute to the source of pain. This results in reduced range of motion secondary to pain and disability in activities that elicit pain.

Radiculopathy

Symptoms include sharp, shooting pain, numbness, and weakness in the arms, corresponding to the affected nerve root. These often follow specific dermatomal patterns, aiding in the identification of the affected nerve root. It can be divided into two types: acute radiculopathy and chronic radiculopathy. Acute radiculopathy mostly occurs in younger age groups with predominant motor symptoms while the latter occurs in older age groups with predominant sensory features. Proper neurological examination and provocative maneuvers like Spurling test exaggerate the symptoms and enable a proper localization of dermatomal distribution.

Myelopathy

Myelopathy is a more severe presentation requiring prompt intervention to prevent permanent damage. Signs and symptoms of myelopathy are usually accompanied by radiculopathy features. Surgery usually proves beneficial across all the cases presenting with myelopathy. Symptoms are usually produced with narrowing of the canal diameter to less than 13 mm.[8] Those with a congenitally narrowed canal often present with such symptoms before development of significant degeneration. Patients usually present with features secondary to involvement of long tract fibers. They present with difficulty in fine motor movements like writing, buttoning of shirts, or typing. Altered sensation is also a common symptom usually involving the extremities. Bowel and bladder involvement occurs late in the disease. On physical examination, patients present with signs of increased tone of limbs, hyperreflexia below the level of compression, Babinski sign, and pathological clonus. Clinically, the severity of myelopathy can be graded using the modified Japanese Orthopaedic Association (mJOA) scale and the functional status can be assessed using the Nurick grading scale.[9,10]

Diagnostic Studies

Plain Radiographs

Sagittal and coronal alignment can be determined from cervical spine radiographs, both anterior and lateral. They can reveal details about the severity of degenerative conditions like spondylolisthesis, osteophyte production, and disk space collapse. Importantly, plain radiographs of the cervical spine taken in flexion and extension can be used to pinpoint any segmental instability that may not have been visible using other static modalities.

CT of Cervical Spine

When evaluating osseous anatomy, CT is a very helpful tool. When used with MRI of the cervical spine, it can be useful in demonstrating the osteophytes which play an important role in stenosis. For patients who have had cervical spine surgery in the past, CT scanning is helpful as an additional tool to evaluate the arthrodesis. If ossification of the PLL is suspected, then also CT proves to be an important modality.

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MRI of Spine

MRI has revolutionized the management of cervical disk disease. The clinician can assess alterations like edema or demyelination inside the spinal cord in addition to the degree of constriction by using various signal acquisition techniques including T1 and T2 weighting. Direct observation of the degenerative changes within the disks is possible; T2-weighted scans clearly show early changes such as desiccation. An MRI can show alterations inside the spinal cord itself as well as a herniated disk or osteophytic spur compressing the cord.

Patients who present with inconclusive imaging findings and have unclear dermatomal distribution may undergo additional tests like neurophysiological tests.

Management Principles

Medical Management

In the vast majority of cases the initial axial neck pain or radiculopathy features will improve with a course of NSAIDs, isometric neck exercises, and cervical bracing. For primary symptoms of neck pain if the above measures fail then a course of muscle relaxant, opioid injection, or even techniques like facet joint injection may be tried. Maintaining appropriate head and neck posture holds utmost importance. Surgical intervention per say is not indicated for neck pain alone. Radiculopathy cases have a positive outcome with addition of neuropathic pain medications like pregabalin or gabapentin. Initial conservative management should be tried in radiculopathy cases with surgery reserved for cases with substantial reduction in neurological function, continuation or worsening of symptoms after a trial of conservative treatment, or recurring or chronic radicular symptoms that have not subsided after 6 weeks. Studies have shown good results with conservative management in radiculopathy.[11] Early call toward surgical management is often reserved for moderate to severe myelopathy.[12]

Surgical Management

Once the decision for surgical management has been decided, the goals of surgery must be kept in mind—alleviating neck and arm pain to improve patient comfort and quality of life, decompression of the spinal cord and neural structures to improve neurological status or prevent further neurological deterioration, and ensuring long-term spinal stability. Both anterior and posterior approaches can be utilized for treatment. The choice between an anterior and a posterior approach is based on several factors. When there is spinal cord compression due to a central and posterolateral disk herniation, an anterior approach is more effective. While anterior techniques deal directly with the pathology, posterior approaches frequently cause an indirect decompression of the spinal cord. Also, some studies have indicated that postoperative cervical lordosis is maintained in patients undergoing anterior approach with fusion. However, some complications unique to anterior approach are dysphagia, hoarseness, vocal cord paralysis, anterior vascular injury, and injury to the trachea or esophagus. Procedures included in anterior approach include ACDF, CDR, and hybrid procedures. For a long time, ACDF has been regarded as the gold standard for treating cervical disk disease and successful results with even three- or four-level surgeries have been reported.[13] CDR has now emerged as a promising modality for treatment for degenerative disk disease ever since the FDA approval of the Prestige, Medtronic, USA, artificial disk in 2007. CDR is also predominantly beneficial for a central or foraminal disease with myelopathy or radiculopathy, and a ventral approach is utilized. When compared to ACDF, the possible benefit of CDR is thought to be a potential decrease in the rate of adjacent-level degeneration through mobility preservation. However, in rare cases

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of CDR, reduced motion might happen as a result of heterotopic ossification. Preliminary results of CDR for single-level degenerative disk disease are promising vis-à-vis ACDF; however, the debate continues regarding the choice between both the procedures.

ACDF

In 1958 Smith and Robinson described their technique for anterior removal of cervical disk material and replacement with a bone graft obtained from the iliac crest.[14] This was the first attempt to access cervical disk pathology via an anterior approach to allow for the development of fusion. After 3 years, Cloward described his technique, in which a diskectomy was performed and a cylindrical bone material was inserted.[3] Over the years, advancements in surgical tools, techniques, and materials have improved the safety and efficacy of ACDF.

ACDF offers several advantages which still make it the gold standard procedure for treating cervical disk disease. ACDF has an extensive history of successful outcomes, supported by numerous studies and decades of clinical experience. The procedure offers reliable and predictable outcomes and results particularly in experienced surgical hands. It offers a high success rate, rendering improvement in patients' neurological symptoms and significant improvement in pain scores. By providing an effective fusion of >90%, it provides robust stabilization which prevents recurrent symptoms due to instability and proves beneficial in cases of segmental instability and deformity.[15–17]

Some potential complications are associated with ACDF. Fusion eliminates movement at the operated segment, which can alter the biomechanics of the cervical spine and place increased stress on adjacent levels, impacting on overall neck flexibility and range of motion. Rare complications reported include risks of nonunion, resulting in persisting symptoms and possible hardware complications such as screw loosening or breakage. An important phenomenon which has been reported in various literature reports is that of adjacent segment disease (ASD) post ACDF surgery. It remains a concerning factor for long-term outcomes of fusion surgeries. By definition, adjacent segment degeneration is radiographic changes of degeneration at levels adjacent to a spinal fusion, and ASD means development of new symptoms correlating with adjacent segment degeneration. At the index level, ACDF is invariably linked to a loss of segmental mobility. One-level ACDF has been shown to result in an average loss of 7 to 8 degrees of angular motion in randomized controlled Food and Drug Administration Investigational Device Exemption (FDA-IDE) trials.[18–22] The more the cervical levels fused the more is the level of instability. Symptomatic ASD has been reported in studies at about 2.9% per year, resulting in approximately 25% patients developing symptoms 7 to 10 years after the procedure.[23] However, Hilibrand and Robbins disputed this notion in 2004 and proposed that an incidence of disease and neighboring segment degeneration following arthrodesis may be related to the natural course of spondylosis.[24] Various other studies have also supported this fact. If fusion is the cause of ASD, then the incidence should be more for multilevel fusions as compared to single level; however, studies don't support this fact. In fact, ASD occurs mainly due to the presence of abnormal end fusion alignment usually kyphosis and not due to motion segment fusion alone.[23,25–29]

Cervical Disk Replacement

Initial ideas for artificial disk replacement emerged in the 1980s, inspired by the success of hip and knee replacements. The Prestige cervical disk, approved in 2007, marked the first FDA-approved artificial cervical disk, paving the way for further innovations in this direction. At present CDR is indicated for adult patients with one- or two-level symptomatic cervical disk protrusions between C3 and C7 that cause radiculopathy or mild myelopathy that is unresponsive to medical therapy.

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Young individuals with radiculopathy from a herniated disk without facet joint arthropathy are the best candidates for cervical arthroplasty. Cervical spine kyphosis or deformity, severe facet joint spondylosis, trauma involving ligamentous or facet injury, osteoporosis, and cervical ankylosis due to spondyloarthropathy are relative contraindications to the procedure.

Technically, cervical arthroplasty becomes more challenging when compared to fusion procedures in view of precise installation of artificial disk in the joint space. Adequate bilateral foraminal decompression is necessary due to the motion-preserving nature of the surgery. Such motion preservation can cause impingement on nerve roots during flexion or extension if the foramina or uncovertebral joints are not adequately decompressed. Important surgical nuances of the procedure include wide decompression of the neural elements, sufficient covering of the end plates by the device, precise height and midline acquisition, and preservation of spinal alignment.[30,31]

Various studies have demonstrated the efficacy and safety of cervical arthroplasty for cervical disk disease.[13,18–21] The most promising and high-quality evidence comparing ACDF and CDR come from the FDA-IDE trials for one- or two-level cervical disk disease. The majority of these studies demonstrated that cervical arthroplasty performed comparably to ACDF, improving neurological status and discomfort following a 7- to 10-year follow-up.[18,20,32–36] At 84 months following arthroplasty, the segmental range of motion (5.2–10.2 degrees) was well preserved. Over 90% of patients were satisfied with the CDR outcome.[36] Both ACDF and CDR have yielded good long-term outcomes for cervical disk disease.[37,38] Additionally, results of CDR are similar for both myelopathy and radiculopathy cases.[39,40]

CDR offers several advantages to the patients undergoing the procedure. CDR preserves the natural motion and biomechanics of the spine. By preserving the natural motion at the involved segments CDR should theoretically reduce the risk of ASD. Almost all studies demonstrate quicker recovery times and early return to normal activities for patients undergoing CDR when compared to fusion surgeries. Arthroplasty correlated with a decreased (but not statistically significant) incidence of ASD in 2- to 5-year outcome studies. Many FDA-IDE trials have shown reduced incidence of both redo surgery and ASD for patients undergoing CDR when compared to ACDF with a follow-up period of 7 to 10 years.[18,20,32,33,35,36] However, statistical significance for the same was reached for only some of the studies while others did not.

Some potential drawbacks associated with CDR include implant-related complications such as implant failure, migration, subsidence (sinking of the implant into the vertebra), and wear and tear. Another major phenomenon observed with arthroplasty includes heterotopic ossification (HO). It refers to ectopic bone formation at the surgical site causing limitation of neck movement and fusion at the index level. Incidence of HO in various trials at 7-10 years follow up was seen to be around 10-13%.[32,33,36] In published literature, kyphosis at the postoperative index level and insufficient end plate covering were associated with a considerably greater incidence of HO.[41] Arthroplasty at multiple levels was also found as a risk factor for development of the same.[42,43] However, further studies and long-term follow-up are needed to elucidate this complication. This raises an important question as to whether CDR is truly a motion-preserving surgery or it is an expensive ACDF spacer. Added to this, there are other concerns, like cost, which also need to be addressed.

The Way Out

Both ACDF and CDR offer good long-term results for management of cervical disk disease. CDR is relatively new but a safe and viable option for disease treatment and is comparable to fusion surgeries. It can achieve good neurological outcomes while

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maintaining segmental mobility. Improvement in quality of life and patient satisfaction are similar in both procedures, with some studies indicating quicker functional recovery for disk arthroplasty. However, the notion that CDR reduces the incidence of adjacent segment degeneration and is a truly motion-preserving surgery needs to be relooked. Current evidence does not support the hypothesis that ACDF causes more ASD or CDR prevents it.[44] Although the reduction of ASD for patients undergoing disk arthroplasty has been reported by several trials, there are many limitations inherently associated with CDR superiority trials.

Most of these trials have a selection bias toward disk arthroplasty cases and not toward ACDF. They are in general industry-sponsored trials with the primary goal of establishing the superiority of disk materials utilized for CDR. The trials were initially blinded to start with but became unblinded at the follow-up of patients, resulting in a tendency to make the outcomes favorable for disk arthroplasty cases. These factors must be kept in mind when deciding the superiority of one treatment over the other. CDR is definitely noninferior to ACDF in properly selected cases of disk disease and in fact has many possible advantages associated with it like minimal or no bracing, faster return to work, and avoidance of iliac crest bone harvest, and some studies even reporting lesser incidence of dysphagia. However, the limitations must also be kept in mind like heterotopic ossification, segmental kyphosis, and hardware-related problems.

Another important factor which still makes ACDF as gold standard for cervical disk disease is its long history in patient management when compared to cervical arthroplasty which is relatively new. Many studies exist in the literature establishing long-term outcomes, and benefits and complications for fusion surgeries[15–17]; however, such robust literature is not available till now for CDR. Still more randomized trials and long follow-up studies are needed to establish the efficacy of disk arthroplasty. As far as costs are considered, both of them are comparable, with ACDF requiring low initial costs as compared to CDR. However, when long-term costs are considered, both of them equalize with studies suggesting that possible costs of redo surgery of fusion cases due to ASD makes it comparable to disk arthroplasty. Another important factor which needs consideration is the familiarity of neurosurgeons. ACDF is preferred by most as being the conventional treatment for disk disease while a slightly longer learning curve and unfamiliarity surrounds the disk arthroplasty procedure especially in developing countries.

Lastly, the most important factor to be kept in mind is proper patient selection. Both the procedures can prove equally beneficial provided proper patient selection criteria are followed. **Table 22.1** highlights the indications, and absolute and relative contraindications of cervical disk arthroplasty. **Table 22.2** depicts the indications of both the surgical arms.

Patients must be explained about both the procedures according to their clinical profile. A thorough preoperative clinico-radiological assessment of the patient is of utmost importance and the possible pros and cons of each surgical arm must be explained to them as well as their caretakers. Informed decision-making is a must when both the surgical procedures are proving to be noninferior and patients' choice must be respected. The need for a timely follow-up at intervals is essential to evaluate the efficacy and complications of either surgery on an individual case-to-case basis.

Conclusion

Cervical disk disease presents a significant challenge in spinal health, impacting patients' quality of life and functional ability. The two primary surgical treatments, CDR and ACDF, offer distinct advantages and disadvantages. Deciding between these procedures involves a comprehensive assessment of the patient's medical history, symptoms, and imaging findings, as well as consideration of patient's

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Table 22.1 Indications, and absolute and relative contraindications of cervical disk arthroplasty

Indications	Absolute contraindications	Relative contraindications
Age >18 years	Severe facet joint degeneration	Ossification of PLL
Failed >6 wk of medical management	Cervical instability with >3.5 mm translation and 11 degrees or more angulation	Congenital spinal stenosis
Symptomatic cervical degenerative disk disease at one or two contiguous levels between C3 and T1 with radiculopathy, myelopathy, or both with critical disk height of at least 3 mm	Severe cervical trauma resulting in disco-ligamentous injury	Multilevel disk disease
	Kyphosis >15 degrees	Neck or arm pain of unknown etiology
	Severe spondylosis	Axial neck pain as a sole presenting symptom
Diagnosis confirmed on radiological imaging	Severe myelopathy	
	Long-term corticosteroid use	
	Malignancy/metastasis/osteoporosis/ other metabolic bone disease/infection	
	Allergy to implant materials	
	Morbid obesity	

Abbreviation: PLL, posterior longitudinal ligament.

Table 22.2 The indications of both the surgical arms

Patient selection	
Consider arthroplasty	**Consider fusion**
• Single-level disease	• Multilevel pathology
• Primarily anterior pathology	• Both anterior and posterior compression
• Preserved segmental motion	• Loss of segmental motion
• Preserved disk space height	• Collapsed disk space
• No significant facet arthropathy	• Segmental ankylosis/significant kyphosis
• Normal cervical alignment	• Osteoporosis/trauma/tumor/infection
	• Segmental instability
	• Previously operated spine

preferences and expectations. Both the procedures have their place in the treatment of cervical disk disease, and the choice should be tailored to each patient's unique needs and circumstances. In conclusion, while ACDF has a proven track record and predictable outcomes, CDR offers the potential for motion preservation and reduced ASD. However, there is no evidence of clear superiority of CDR over ACDF. It is just a good alternative in properly selected cases. Various factors highlighted in the literature have still not rendered disk arthroplasty to be the gold standard procedure for cervical disk disease management. Ongoing research and long-term studies will continue to refine these surgical options, ultimately improving patient care and outcomes in the treatment of cervical disk disease.

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References

1. Stookey B. Compression of the spinal cord due to ventral extradural cervical chondromas. Arch Neurol Psychiatry 1928;20(2):275–291
2. Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 1934;211(5):210–215
3. Cloward RB. The anterior approach for removal of ruptured cervical disks. J Neurosurg 1958; 15(6):602–617
4. Tampier C, Drake JD, Callaghan JP, McGill SM. Progressive disc herniation: an investigation of the mechanism using radiologic, histochemical, and microscopic dissection techniques on a porcine model. Spine 2007;32(25):2869–2874
5. Lawrence JS. Disc degeneration. Its frequency and relationship to symptoms. Ann Rheum Dis 1969;28(2):121–138
6. Boden SD, McCowin PR, Davis DO, Dina TS, Mark AS, Wiesel S. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72(8):1178–1184
7. Bovim G, Schrader H, Sand T. Neck pain in the general population. Spine 1994;19(12):1307–1309
8. Yue WM, Tan SB, Tan MH, Koh DC, Tan CT. The Torg—Pavlov ratio in cervical spondylotic myelopathy: a comparative study between patients with cervical spondylotic myelopathy and a nonspondylotic, nonmyelopathic population. Spine 2001;26(16):1760–1764
9. Tetreault L, Kopjar B, Nouri A, et al. The modified Japanese Orthopaedic Association scale: establishing criteria for mild, moderate and severe impairment in patients with degenerative cervical myelopathy. Eur Spine J 2017;26(1):78–84
10. Nurick S. The natural history and the results of surgical treatment of the spinal cord disorder associated with cervical spondylosis. Brain 1972; 95(1):101–108
11. Sampath P, Bendebba M, Davis JD, Ducker T. Outcome in patients with cervical radiculopathy. Prospective, multicenter study with independent clinical review. Spine 1999;24(6):591–597
12. Fehlings MG, Wilson JR, Kopjar B, et al. Efficacy and safety of surgical decompression in patients with cervical spondylotic myelopathy: results of the AOSpine North America prospective multi-center study. J Bone Joint Surg Am 2013;95(18):1651–1658
13. Chang SW, Kakarla UK, Maughan PH, et al. Four-level anterior cervical discectomy and fusion with plate fixation: radiographic and clinical results. Neurosurgery 2010;66(4):639–646, discussion 646–647
14. Smith GW, Robinson RA. The treatment of certain cervical-spine disorders by anterior removal of the intervertebral disc and interbody fusion. J Bone Joint Surg Am 1958;40-A(3):607–624
15. Boakye M, Mummaneni PV, Garrett M, Rodts G, Haid R. Anterior cervical discectomy and fusion involving a polyetheretherketone spacer and bone morphogenetic protein. J Neurosurg Spine 2005;2(5):521–525
16. Mummaneni PV, Haid RW. The future in the care of the cervical spine: interbody fusion and arthroplasty. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine 2004;1(2):155–159
17. Tumialán LM, Pan J, Rodts GE, Mummaneni PV. The safety and efficacy of anterior cervical discectomy and fusion with polyetheretherketone spacer and recombinant human bone morphogenetic protein-2: a review of 200 patients. J Neurosurg Spine 2008;8(6):529–535
18. Burkus JK, Traynelis VC, Haid RW Jr, Mummaneni PV. Clinical and radiographic analysis of an artificial cervical disc: 7-year follow-up from the Prestige prospective randomized controlled clinical trial: clinical article. J Neurosurg Spine 2014;21(4):516–528
19. Heller JG, Sasso RC, Papadopoulos SM, et al. Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion: clinical and radiographic results of a randomized, controlled, clinical trial. Spine 2009;34(2):101–107
20. Janssen ME, Zigler JE, Spivak JM, Delamarter RB, Darden BV II, Kopjar B. ProDisc-C total disc replacement versus anterior cervical discectomy and fusion for single-level symptomatic cervical disc disease: seven-year follow-up of the prospective randomized U.S. food and drug administration investigational device exemption study. J Bone Joint Surg Am 2015;97(21):1738–1747
21. Mummaneni PV, Burkus JK, Haid RW, Traynelis VC, Zdeblick TA. Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: a randomized controlled clinical trial. J Neurosurg Spine 2007;6(3):198–209
22. Upadhyaya CD, Wu JC, Trost G, et al. Analysis of the three United States Food and Drug Administration investigational device exemption

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cervical arthroplasty trials. J Neurosurg Spine 2012;16(3):216–228
23. Hilibrand AS, Carlson GD, Palumbo MA, Jones PK, Bohlman HH. Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. J Bone Joint Surg Am 1999;81(4):519–528
24. Hilibrand AS, Robbins M. Adjacent segment degeneration and adjacent segment disease: the consequences of spinal fusion? Spine J 2004;4(6, Suppl):190S–194S
25. Cho SK, Riew KD. Adjacent segment disease following cervical spine surgery. J Am Acad Orthop Surg 2013;21(1):3–11
26. Levin DA, Hale JJ, Bendo JA. Adjacent segment degeneration following spinal fusion for degenerative disc disease. Bull NYU Hosp Jt Dis 2007;65(1):29–36
27. Hwang SH, Kayanja M, Milks RA, Benzel EC. Biomechanical comparison of adjacent segmental motion after ventral cervical fixation with varying angles of lordosis. Spine J 2007;7(2):216–221
28. Ozer E, Yücesoy K, Yurtsever C, Seçil M. Kyphosis one level above the cervical disc disease: is the kyphosis cause or effect? J Spinal Disord Tech 2007;20(1):14–19
29. Kolstad F, Nygaard ØP, Leivseth G. Segmental motion adjacent to anterior cervical arthrodesis: a prospective study. Spine 2007;32(5):512–517
30. Tu TH, Chang CC, Wu JC, Fay LY, Huang WC, Cheng H. Resection of uncovertebral joints and posterior longitudinal ligament for cervical disc arthroplasty. Neurosurg Focus 2017;42(VideoSuppl1):V2
31. Chang CC, Wu JC, Chang PY, et al. Stepwise illustration of teeth-fixation semi-constrained cervical disc arthroplasty. Neurosurg Focus 2017; 42(VideoSuppl1):V4
32. Lanman TH, Burkus JK, Dryer RG, Gornet MF, McConnell J, Hodges SD. Long-term clinical and radiographic outcomes of the Prestige LP artificial cervical disc replacement at 2 levels: results from a prospective randomized controlled clinical trial. J Neurosurg Spine 2017;27(1):7–19
33. Gornet MF, Burkus JK, Shaffrey ME, Nian H, Harrell FE Jr. Cervical disc arthroplasty with prestige LP disc versus anterior cervical discectomy and fusion: seven-year outcomes. Int J Spine Surg 2016;10:24
34. Gornet MF, McConnell JR, Riew KD, et al. Treatment of cervical myelopathy: long-term outcomes of arthroplasty for myelopathy versus radiculopathy, and arthroplasty versus arthrodesis for myelopathy. Clin Spine Surg 2018;31(10):420–427
35. Phillips FM, Geisler FH, Gilder KM, Reah C, Howell KM, McAfee PC. Long-term outcomes of the US FDA IDE prospective, randomized controlled clinical trial comparing PCM cervical disc arthroplasty with anterior cervical discectomy and fusion. Spine 2015;40(10):674–683
36. Radcliff K, Davis RJ, Hisey MS, et al. Long-term evaluation of cervical disc arthroplasty with the Mobi-C© cervical disc: a randomized, prospective, multicenter clinical trial with seven-year follow-up. Int J Spine Surg 2017;11(4):31
37. Mehren C, Heider F, Siepe CJ, et al. Clinical and radiological outcome at 10 years of follow-up after total cervical disc replacement. Eur Spine J 2017;26(9):2441–2449
38. Mummaneni PV, Amin BY, Wu JC, Brodt ED, Dettori JR, Sasso RC. Cervical artificial disc replacement versus fusion in the cervical spine: a systematic review comparing long-term follow-up results from two FDA trials. Evid Based Spine Care J 2012;3(S1):59–66
39. Chang HK, Huang WC, Wu JC, et al. Should cervical disc arthroplasty be done on patients with increased intramedullary signal intensity on magnetic resonance imaging? World Neurosurg 2016;89:489–496
40. Fay LY, Huang WC, Wu JC, et al. Arthroplasty for cervical spondylotic myelopathy: similar results to patients with only radiculopathy at 3 years' follow-up. J Neurosurg Spine 2014;21(3):400–410
41. Tu TH, Wu JC, Huang WC, Wu CL, Ko CC, Cheng H. The effects of carpentry on heterotopic ossification and mobility in cervical arthroplasty: determination by computed tomography with a minimum 2-year follow-up: clinical article. J Neurosurg Spine 2012;16(6):601–609
42. Chang PY, Chang HK, Wu JC, et al. Differences between C3-4 and other subaxial levels of cervical disc arthroplasty: more heterotopic ossification at the 5-year follow-up. J Neurosurg Spine 2016;24(5):752–759
43. Wu JC, Huang WC, Tsai TY, et al. Multilevel arthroplasty for cervical spondylosis: more heterotopic ossification at 3 years of follow-up. Spine 2012; 37(20):E1251–E1259
44. Sasso RC, Smucker JD, Hacker RJ, Heller JG. Clinical outcomes of BRYAN cervical disc arthroplasty: a prospective, randomized, controlled, multicenter trial with 24-month follow-up. J Spinal Disord Tech 2007;20(7):481–491

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23 Role of Anterior versus Posterior Approach for Cervical Spondylotic Myelopathy—A Narrative Review

Hemant Bhartiya, Sushil Patkar, Chandan Mohanty, Vivek Vaid, Sankalp Bhartiya, Akshay Mangal and Pradnya Patkar

Introduction

Cervical spondylosis is one of the most common degenerative problems of ageing, with a prevalence of 15% at 34 years of age, 60% at 54 years, and 90% at 65 years and older.[1] Cervical spondylosis is characterized by osteophyte formation, cervical disk, ossified posterior longitudinal ligament, and hypertrophy of ligamentum flavum. This may be associated with subluxation, cervical cord changes in the form of gliosis or atrophy of the cord, loss of normal lordotic curve, decreased vertebral height (disk space reduction), and vascular compromise.[2]

Surgery is the most efficacious modality of treatment for moderate and severe cervical spondylotic myelopathy (CSM). Current guidelines recommend the surgical management of patients with moderate (modified Japanese Orthopedic Association [mJOA] 12–14) to severe (mJOA ≤11) degenerative cervical myelopathy (DCM), while there is controversy surrounding the management of patients with mild DCM (mJOA 15–17).[3] Emerging evidence also shows the effectiveness of surgery in the management of progressive mild CSM. CSM can be treated by both anterior and posterior cervical approaches. Anterior approaches include diskectomy, corpectomy, and a hybrid of both these procedures. Posterior approaches include laminectomy, laminoplasty, laminectomy, and fusion. Emerging approaches include artificial disk replacement, minimally invasive techniques, fusion without decompression, etc. There have been numerous publications which have compared the efficacy of anterior and posterior approaches for CSM.

In this chapter, the authors give a broad overview of the anterior and posterior approaches and discuss the current evidence regarding indications, contraindications, complications, and outcomes of each in comparison with each other.

Pathophysiology

Cervical spondylosis is a progressive pathologic process that is secondary to biomechanical stress and strain. The process includes disk degeneration, facet arthropathy, and pathologic changes such as hypertrophy or ossification within both the posterior longitudinal ligament and the ligamentum flavum.[4]

The cervical spine has a lordotic alignment that plays an important role in load sharing. Cervical lordosis places the force vector over the central axis of the spine. The ageing process leads to degenerative changes related to repetitive mechanical forces that can be

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compounded by traumatic events. Progressive degeneration leads to laxity within ligaments and facetal joints, leading to spondylolisthesis and straightening of the cervical curvature. Ligamentous and facet hypertrophy ensues, and biomechanical stress between adjacent end plates leads to osteophyte formation. The force vector shifts anteriorly due to the loss of lordosis, placing further stress on the already diseased disk spaces. These degenerative changes of disk bulging/herniation, uncovertebral and facet osteophyte formation, and ligamentous hypertrophy can induce neurological symptoms secondary to compression.[1]

Conservative Management

Myelopathy

There is not enough evidence to suggest and predict the natural history of CSM.[1,5] There are very few conservative options that are likely to significantly alter the long-term progression of the disease. Most surgeons would recommend at least close serial radiographic and clinical follow-up, with surgical intervention being strongly considered if there is evidence of disease progression (**Fig. 23.1**). A significant number of patients may deteriorate clinically with conservative management.[6] Another drawback of conservative management is that in the presence of significant spinal cord compression, there also exists the risk of a catastrophic neurological deterioration in the event of cervical trauma that otherwise may have been insignificant.

Surgical Approaches

CSM is broadly treated surgically either by anterior or posterior approach. The decision as to which surgical approach to employ depends on three main factors.

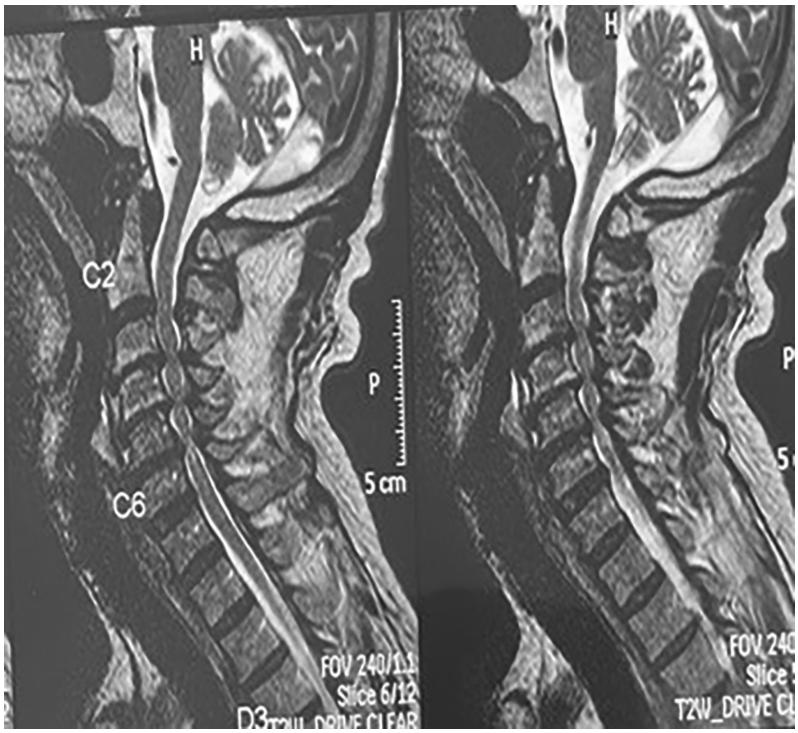

Fig. 23.1 Multiple-level degenerative cervical spondylotic myelopathy (the patient did not consent for surgery; at 15 years follow-up, the patient has difficulty in walking and stooping forward).

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Site of Compression

Degenerative disease with congenitally narrow canal (diameter <12 mm):

- Dorsal compression: Posterior approach.
- Ventral compression: Anterior approach.

Levels

- Less than three levels: Anterior approach.
- More than three levels: Posterior approach.

The anterior approach is more demanding for multiple levels than laminectomy or laminoplasty. In older patients with stiffness or ankylosis, decompression may be sufficient. As younger patients with a full range of movement are at risk of swan neck deformity at a later stage, lateral mass fixation and posterolateral fusion should be done.

Curvature (Fig. 23.2)

- Lordosis + Dorsal compression + >3 levels: Posterior approach.
- Lordosis + Ventral compression + <3 levels: Anterior approach.
- Kyphotic deformity: Anterior approach.

Posterior Approach

Advantages

- Avoids neurovascular and visceral structures.
- Can be extended cranially or caudally as required.
- Decompression may be achieved without compromising cervical spine motion, as effective decompression may be achieved without fusion.
- Less blood loss.

Disadvantages

- Difficulty in addressing more ventral disease.
- Failure to address kyphosis.
- Increased postoperative pain.
- Higher infection rate.

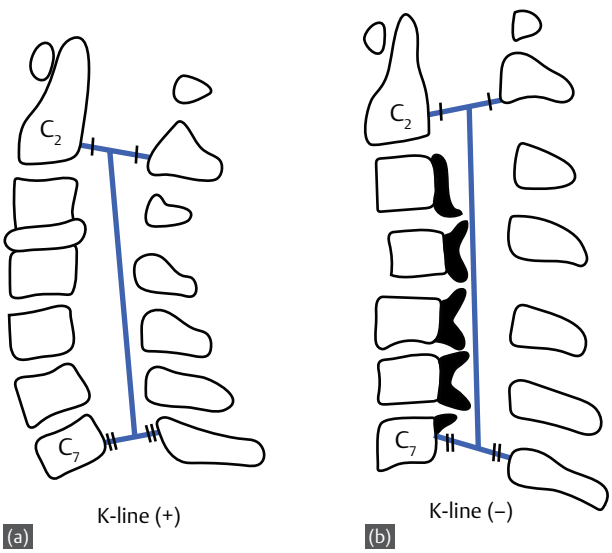

Fig. 23.2 Modified K-line[7]: Illustration of a midsagittal cervical spine with preserved lordosis **(a)** and kyphosis **(b)**. A line has been drawn from the midpoint of the cervical cord at C2 to the midpoint of the cervical cord at C7. If any portion of the osteophytes, disk, or ossification of the posterior longitudinal ligament (OPLL) crosses or lies within 4 mm of the line then the cervical spine is said to have an "effective" kyphosis, and an anterior decompressive approach is generally indicated. Conversely, if the anterior compression is >4 mm away from the modified K-line, the cervical spine is considered to have a lordotic configuration, and a posterior decompression approach is generally preferred.[7]

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If the disease extends more than three levels, then the posterior approach is preferable in degenerative disease with congenital narrow canal (diameter <12 mm) and for ossification of the posterior longitudinal ligament (OPLL) as the ventral dura is frequently densely adherent to the ossified ligament, and it would invariably lead to cerebrospinal fluid (CSF) leak unless OPLL floating technique is employed in the anterior approach[1] (**Fig. 23.3**).

Anesthesia, Positioning, and Surgical Principles

General anesthesia is used, and it is mostly done in a prone position with horseshoe head holder. When positioning, the patient's eyes should be well protected, and head kept in a slightly flexed position.

After meticulous skin preparation, midline skin incision is made. Then, with the cutting cautery, the avascular plane is identified up to spinous processes and then the lamina of both sides is exposed subperiosteally. If only laminectomy is to be done, then there is no need to expose the lateral masses. When laminectomy with fixation is planned, the lateral masses and facet joints are exposed at all levels. For laminoplasty, lateral masses are exposed with preservation of the facet capsule. After exposure, a small trough is made with 2- or 3-mm burr and the trough is extended through the whole length of the levels to be decompressed at the junction of laminae and the facet on both sides, and the laminae are removed (**Fig. 23.4**).

For laminoplasty full thickness trough is drilled on one side and upto ventral cortex on the side to be hinged as we need to hinge open the trough, it should be straight so the laminae do not overlap or compress the cord and the depth should be up to ventral cortex. Cortex at the rostral and caudal aspect of the laminae should be removed. Ligamentum flavum is then cut at the rostral and caudal ends. Laminoplasty is then gradually opened with some pressure at two or more points on the spinous processes. A small curette at the midpoint may help to lift the laminae from the cord. An opening of 3-5 mm is desirable. Small titanium plates one above and one below are fixed from lamina to lateral mass to keep

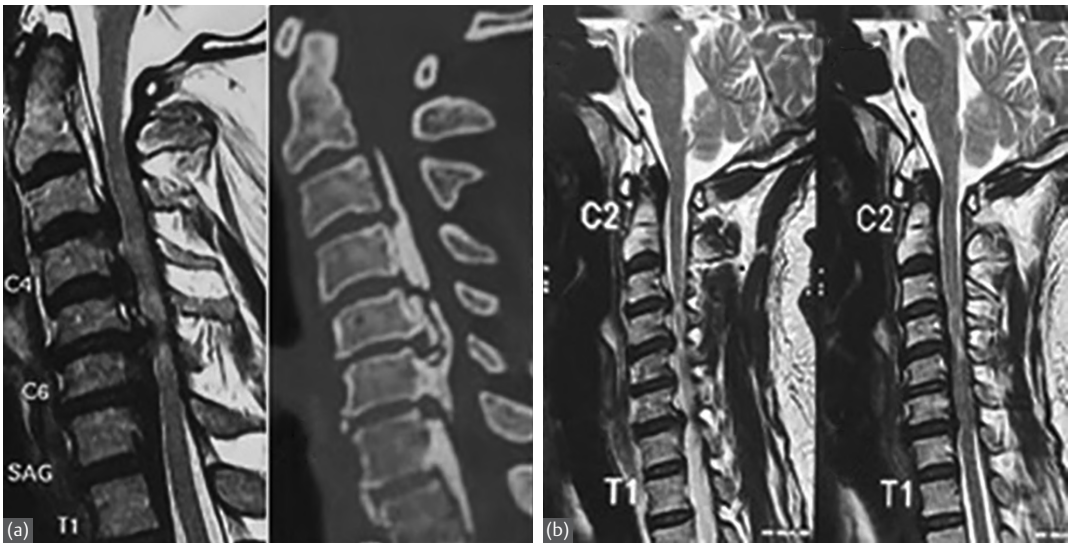

Fig. 23.3 **(a)** Multilevel ossification of the posterior longitudinal ligament (OPLL). **(b)** Multilevel cervical disk.

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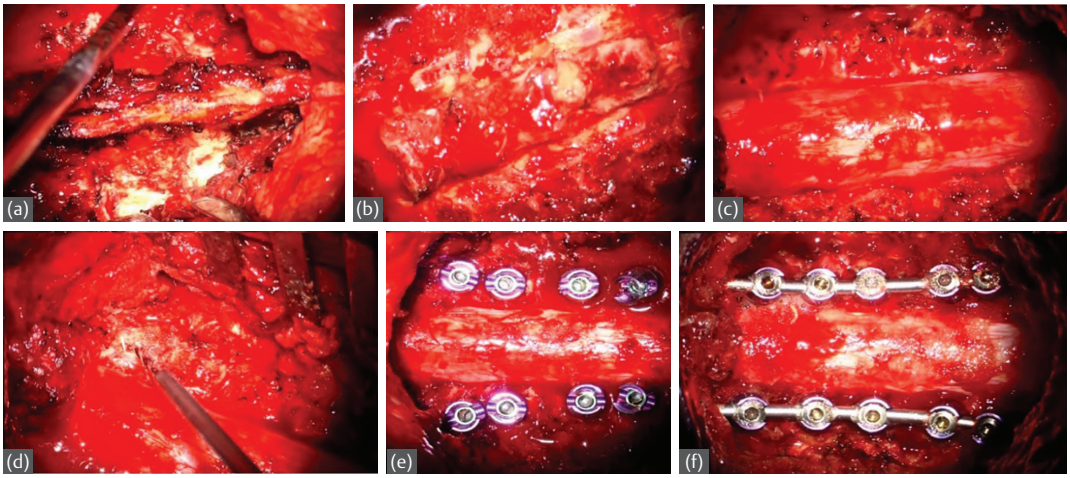

Fig. 23.4 **(a)** Spinous process and then laminae exposed subperiosteally. **(b)** Trough is made on both sides. **(c)** Laminectomy done with cord decompressed up to roots. **(d)** Points of screw entry by twist drill. **(e)** Screws are then placed through an entry point in the standard trajectory. **(f)** Rod is contoured to achieve a satisfactory spinal alignment.

Fig. 23.5 C2–C6 ossification of the posterior longitudinal ligament (OPLL) with severe cord compression. **(a)** Preoperative MRI. **(b)** Postoperative MRI. **(c)** Postoperative X-ray showing plate fixation (arrow sign) at C4 and C6.

laminoplasty open. Alternatively, we used to put bone taken from the spinous process in the opening and fix it with wire or suture (**Fig. 23.5**).

For laminectomy both sided troughs are drilled up to ventral cortex through the length of the laminectomy planned and when thin bone left, it is removed by a small curette or 1mm punch. Ligamentum flavum at rostral and caudal ends are cut and laminae lifted from below up. Ligamentum flavum laterally is also cut. Care is taken that the rostral point does not impinge on the cord when lifting the cut laminae. Some surgeons prefer sitting position. the advantage is avascular field and better visualisation of cervico thoracic field

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on fluoroscopy but due to more time taken in positioning and risk of air embolism, surgeon prefer prone position. If sitting position is done then a precordial doppler and an end tidal CO2 monitoring is required.

Lateral Mass Screw Fixation

C3 to C6 levels are mostly fixed. When C7 is to be fixed then the screws are placed through large pedicles as the lateral mass of C7 is thin and obliquely angled.

The optimum screw is 3.5-4 mm in diameter and 16mm in length.

After decompressive laminectomy we follow the roots to the foramen as they give a reasonably good idea about the pedicle.

Then the lateral mass screw is placed and directed anteriorly, superiorly and laterally towards the safest upper quadrant of the lateral mass. An idea of foramen transversarium can be obtained by looking at the axial cuts of the CT scan. Sometimes the lateral mass is severely degenerated and dystrophic. In these cases, transpedicular screws can also be placed. Different authors have suggested different entry points but the aim in all is a safe trajectory directed anteriorly, laterally and rostrally as shown in the picture to prevent injury to vertebral artery or the nerve root.

Multiaxial screws are used as they can accommodate some sagittal and coronal alignment. The rods are contoured to match sagittal alignment and secured by screws (**Figs. 23.4, 23.6**, and **23.7**).

Complications and Outcome

It is best to avoid complications from intubation to reversal of the patient. During intubation, extreme extension/flexion should be avoided and done in a neutral position. In the case of restricted or difficult cases, fiberoptic intubation may be done. The patient should be operated on normotensive pressure. Deterioration in motor power is reported in up to 8% of patients.[8,9] C5 palsy is the most common, and less common is C6 palsy. They are manifested with weakness in lifting the shoulder, representing deltoid and biceps weakness. Vertebral artery injury, when it lies anterior to the medial half of lateral mass, is best avoided by properly directed screws, and if vertebral artery injury is suspected, it is better to avoid further procedure. For tamponade, a smaller screw should be placed.

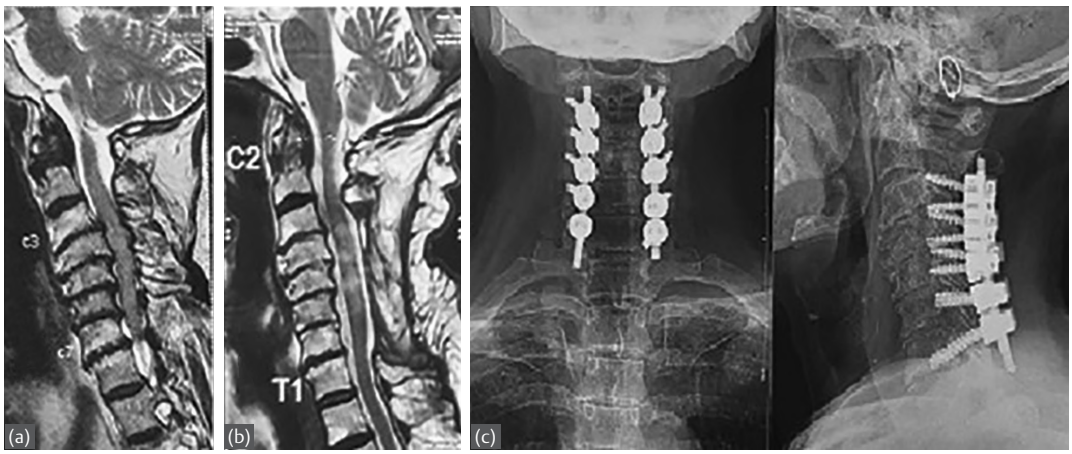

Fig. 23.6 **(a)** Multiple-level compression with loss of normal lordotic curvature. **(b)** Postoperative MRI showing some restoration; alignment of vertebral bodies and ventral and dorsal subarachnoid spaces seen well. **(c)** Posterior decompression with lateral mass fixation.

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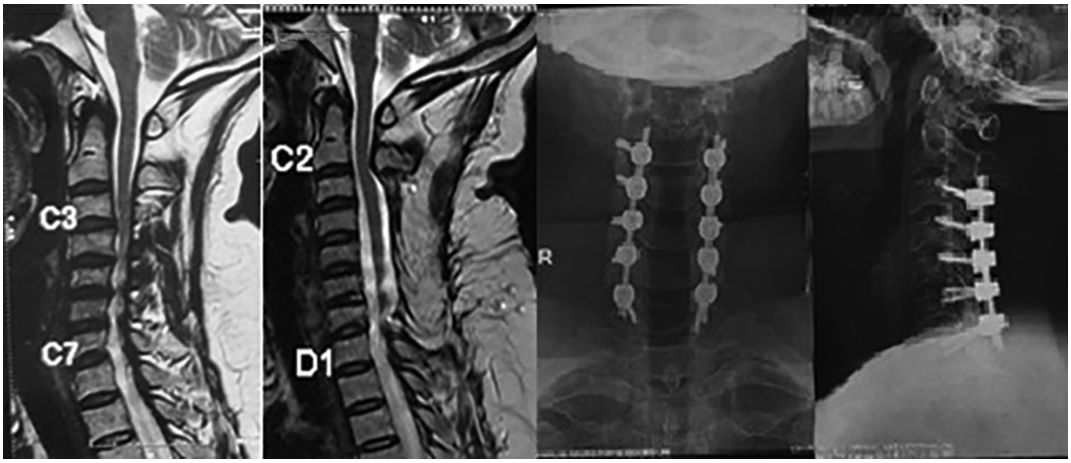

Fig. 23.7 Multiple-level compression; posterior decompression with lateral mass fixation.

Immediate angiogram after completing the procedure should be done, and if dissection is seen, a stent may be placed.

The outcome depends on the age, preoperative neurological grading, and duration of symptoms—shorter duration of symptoms and less symptomatic cases have better results.[10]

Selection of Anterior Approach

The cervical spine geometry and the predominant orientation of the neural compression are the two main aspects of the disease which should be taken into account; the presence of either of these aspects suggests the use of a ventral surgical approach.[11] The anterior cervical approach is preferred if the compressive pathology is primarily ventral, primarily localized to an interspace or interspaces, and/or associated with cervical instability, spondylolisthesis, or a kyphotic deformity and neck pain.[12]

Techniques of Anterior Surgery for CSM

Various surgical techniques such as anterior cervical diskectomy and fusion (ACDF) with or without instrumentation, anterior cervical corpectomy and fusion (ACCF) with or without instrumentation, oblique corpectomy (OC), cervical disk replacement/arthroplasty (CDR), ACDF + ACCF (skip technique), partial corpectomy, and hybrid technique (ACDF + CDR) have been described in the literature with similar results and technique-specific complications.[13]

Anterior Cervical Diskectomy and Fusion (ACDF)

In single-level ventral compression with focal kyphosis, ACDF is the procedure of choice. Good microsurgical techniques with microdrill and curettes enable thorough removal of posterior osteophyte or OPLL and the posterior longitudinal ligament (PLL).[14] Proper preparation ("gardening") of the end plates to permit cancellous bone migration by creeping substitution into the interbody spacer is mandatory to enhance the fusion. Keystoning the recipient bed with proper sizing of the spacer (without over-distraction) to achieve locking of the interbody reconstruction material reduces graft/implant loosening (**Fig. 23.8**). Auto graft (gold standard), allograft, cage (titanium, polyether-ether ketone [PEEK]), and recently, the zero-profile cages with integrated screws are the reconstruction

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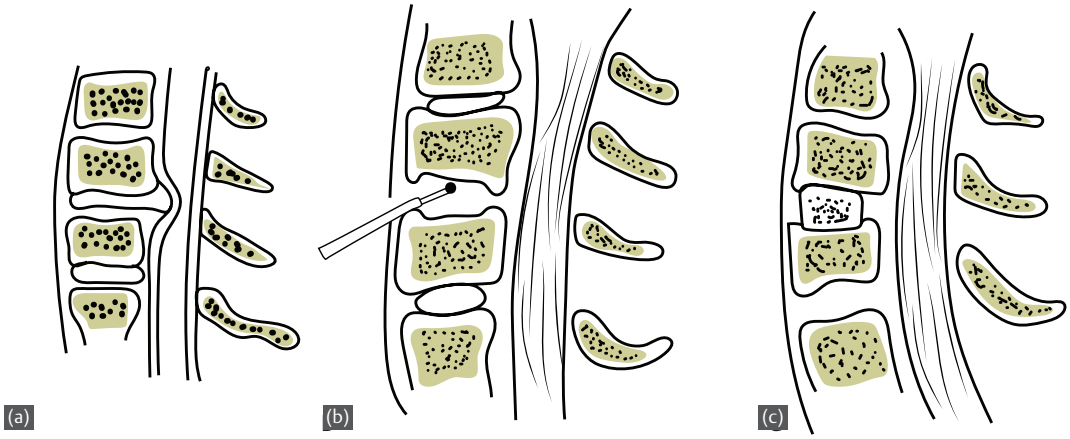

Fig. 23.8 **(a)** Ventral cord compression secondary to disk herniation. **(b)** End plate preparation with curette. **(c)** Keystone preparation of the end plate with an appropriate size graft.

options to get a fusion and restore lordosis.[15] Anterior plating is not required in single-level ACDF surgery. ACDF has shown good results over the years in many studies. Adjacent-level degeneration (adult degenerative scoliosis adjacent segment degeneration [ASD]) after ACDF has an incidence of 3% per year and up to 25% in 10 years and remains an issue. It seems to be technique-related or a part of the age-related degeneration of the spine. Rigid fixation, plate encroachment on adjacent disks, fusion failure, and failure to correct the lordosis are some reasons for the problem.[15] The recently popular zero-profile PEEK cages with integrated screws avoid the plate, further decreasing the chances of ADS[16] (**Fig. 23.9**).

Fig. 23.9 Zero-profile anterior cervical interbody polyether-ether ketone (PEEK) cage with integrated screws.

Anterior Cervical Corpectomy and Fusion with Fixation (ACCF)

Corpectomy is required in cases where the compressive pathology is not confined to the disk space region and extends behind the vertebral bodies above or below and in cases with significant ventral compression by the segmental OPLL.[17] After performing diskectomies on either side of the bodies to be removed, the uncinate processes are identified by dissecting the longus coli laterally, and they are the lateral limit (to protect the vertebral arteries) for creating a longitudinal trough in the bodies to be excised. This trough is deepened to reach the PLL, first at the mid-body level of each vertebra, and once the epidural space is reached, the end plate margins are removed with curettes and fine Kerrison

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punches. The end plate of the preserved vertebrae on either side of the corpectomy is gardened for graft fusion. Reconstruction of the defect is performed with iliac crest strut, fibula, or metallic cages (**Fig. 23.10**). Anterior plates are always used for more than one level corpectomy following corpectomy to prevent dislodgement of the interbody strut. Making drill holes in the lateral aspect of the iliac strut graft or the fibula is an important step to enhance fusion. Expandable cages (the poorest construct due to floating minimal bone graft from the corpectomy when distracted) with/without integrated screws at either end are becoming popular due to ease, but long-term results are lacking.[18,19]

Corpectomy permits a more satisfactory decompression in canal stenosis where the compressive elements extend beyond the disk margins into the retrovertebral space.

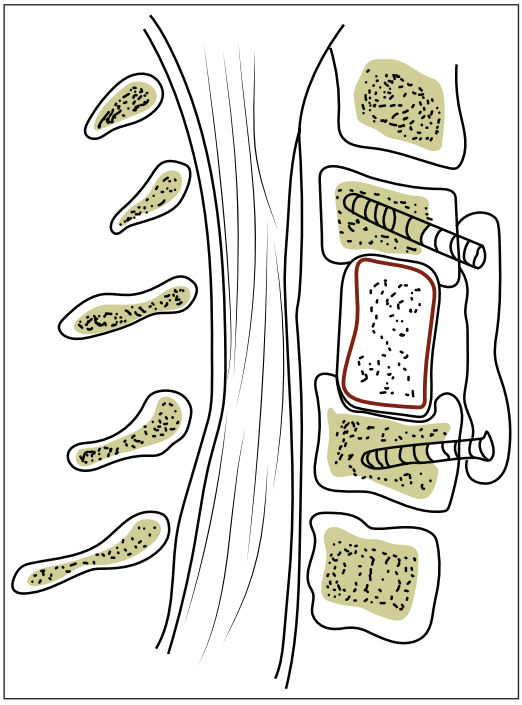

Fig. 23.10 Reconstruction of the corpectomy defect with iliac crest graft and anterior cervical plate and screws.

ACCF has been demonstrated to be clinically effective for single-level or two-level diseases. Potential advantages of corpectomy-based approaches include complete decompression, especially with significant stenosis directly behind the vertebral body, fewer bone–graft interfaces, and potentially greater surface area for fusion to occur. Beyond two-level ACDF, ACCF has a better fusion rate.

Beyond three-level corpectomy, early dislodgement is a potential risk. The anterior plate creates a long lever arm with fixation at either end with a potential to fail in more than 50% of cases.[20,21] Many authors recommend additional posterior fixation in lordosis for additional security.[22] Graft dislodgement is also a function of surgical technique, and even long three-level defects have been successfully fused using fibular struts.[23]

A hybrid technique which combines a one-level corpectomy with a one-level diskectomy has demonstrated less bleeding, superior restoration of segmental lordosis, better segmental stability, and higher fusion rates than two-level corpectomy.[24]

In multilevel compression, the "skip" technique is a good option and involves two separate corpectomies with an intact body in between. The skip corpectomy is indicated for compressions extending from C3–C4 to C6–C7 and involves corpectomy at C4 and C6 with preservation of the C5 vertebral body for segmental fixation. This technique has been reported to have better fusion rates and fewer implant failures as compared to three-level corpectomies.[25,26]

Cervical Disk Replacement (CDR)

In recent years, arthroplasty has become increasingly popular to treat myelopathy, especially in younger patients with single-level disease. The probability of motion preservation and avoiding ADR have been the reasons for this option. Literature has shown noninferiority in many studies, and more long-term evidence with a larger sample size is necessary.[27,28]

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Anterior versus Posterior Surgery for CSM: Challenges and Current Evidence

Challenges

A true comparison of all the types and subtypes of anterior and posterior approaches is difficult, given the heterogeneity of the surgical procedures. Some of the posterior approaches described in the literature include laminectomy alone, fixation alone, laminectomy with posterior instrumented fusion, laminoplasty and all its subtypes, newer minimally invasive decompression techniques, etc. Similarly, anterior approaches include diskectomy, multilevel diskectomy, single or multilevel corpectomies, oblique corpectomy, hybrid of diskectomy with corpectomy, cervical disk arthroplasty, minimally invasive anterior decompression etc. This factor has to be carefully considered before interpreting the results of any comparison between anterior and posterior approaches.

CSM is an extremely heterogeneous disease where the postoperative outcome is dependent on baseline neurological status, age, duration of symptoms, smoking status, physical/psychological comorbidities, presence of T1-weighted hypointensity, combined T1- and T2-weighted signal changes, or greater number of levels of T2-weighted hyperintensity, low apparent diffusion coefficient (ADC) and fractional anisotropy (FA), and disruption of long tracts on DTI imaging.[29,30] Duration of the disease and the baseline neurological status are the most important determinants of surgical outcome. The surgical approach may be one of the important factors determining the outcome, but it is not the only factor defining the overall outcome. Therefore, all these factors may need to be matched before a true comparison of both the surgical approaches can be made.

The surgical complication profiles of the anterior and posterior approaches are quite different. The main complications with anterior approaches include dysphagia and hoarseness of voice.[31] On the other hand, the main complications with posterior approaches are postoperative pain and a higher incidence of neurological deterioration.[31]

In addition, there are definite regional variations in the selection of the type of surgical approaches. In a survey of North American surgeons, it was seen that about 70% of the surgeons preferred a laminectomy with instrumentation as a preferred posterior modality for CSM,[32] whereas a similar survey in the Asia-Pacific region showed that the preferred posterior approach for 64% of surgeons was laminoplasty.[33]

Current Consensus and Evidence

Ghogawala et al performed a randomized controlled trial (RCT) to compare the role of anterior and posterior approaches to CSM.[31] This RCT showed that both the anterior and posterior surgeries for CSM showed similar patient-reported physical functioning at 1 year after surgery. Another systematic review published before this RCT seemed to indicate that anterior approaches led to a better JOA recovery and neurological recovery but had a higher complication rate and operation time compared to the posterior approach.[34] Similarly, it was shown that DCM patients with kyphosis had a better neurological recovery with the anterior approach.[35] A randomized trial by El-Ghandour and coworkers also showed similar neurological outcomes and patient satisfaction rates with both the approaches, but the anterior surgery group had better results in terms of postoperative neck pain (visual analog scale [VAS] and neck disability index [NDI] scores), while the posterior group showed shorter operating time and absence of dysphagia but a longer hospital stay.[36]

Somewhat contrary to other papers, Nunna and coworkers, in a retrospective

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registry-based analysis, showed that posterior approaches have a higher complication rate, higher short- and long-term narcotic use, and higher revision surgery rate.[37] In a database analysis of 1151 patients, the authors noted two-thirds of the patients underwent anterior surgery, and one-third of the patients underwent posterior surgery with marked baseline differences in patient parameters. After adjusting for these differences, the authors reported a significant improvement in NDI at short- and long-term follow-up.[38]

The World Federation of Neurosurgical Societies (WFNS) recommendations in 2019 suggested that the complication rate of anterior surgeries for CSM varies from 1.6 to 31.3%.[39] Improvement after anterior surgery for CSM has been reported in 70 to 80% of patients. JOA recovery rates are around 60 to 70%. These outcomes are also seen in long-term follow-up studies and appear to be durable. The success rates appear to be similar for the different forms of anterior surgery.[39] Kwok et al suggested that the anterior approach is preferred for K-line (−) OPLL, K-line (+) with canal-occupying ratio >60%, and DCM with pre-existing cervical kyphosis.[40] The posterior approach is preferred for K-line (+) OPLL with canal-occupying ratio <50 to 60%, and multilevel CSM. No particular advantage for either approach was observed for DCM in a lordotic cervical spine.[40] The anterior approach is generally associated with more complications and thus needs to be weighed carefully during decision-making.

Multiple other authors have also corroborated the fact that in terms of neurological outcomes, both the approaches are similar, which is in line with the papers discussed above.[17,41,42] In a very recent paper published in 2023, three-level ACDF was compared to posterior cervical fixation in a prospective database analysis.[43] The authors noted a higher patient satisfaction rate with three-level ACDF but similar outcomes in the patient's functional status indices with a follow-up of 2 years. The authors also noted more blood loss and longer hospitalization in posterior approaches compared to ACDF.[43]

However, the lack of high-quality RCTs limits the strength of the recommendations made by the various papers.

Finally, the choice between anterior and posterior approaches is based on patient-specific anatomic factors, including (1) the primary location of the compressive pathology (ventral versus dorsal), (2) the regional sagittal alignment, (3) the extent of disease involvement, (4) the presence of preoperative neck pain, and (5) the presence of congenital stenosis (**Table 23.1**).

In our massive country, CSM requiring surgery is a common problem and is increasing in incidence with increasing longevity. Lack of disease awareness, late presentation, extensive diversity in locally available facilities, and financial considerations are some of the challenges facing us. Joint decision-making with the patient and relatives is necessary to explain the complexities of surgical decision-making and to calibrate patient outcomes to patient expectations.

Conclusion

Anterior and posterior approaches both achieve excellent neurological outcomes. However, they also have a distinct complication profile. There are no definitive guidelines for choosing one approach over the other and the decision to select one approach over the other is based on the individual case profile.

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Table 23.1 Recommendations for anterior and posterior surgeries for CSM

Approach	Indications	Complications and contraindications
ACDF	• One- to two-level disease • Ventral pathology (disk, osteophytes, OPLL) • Rigid cervical kyphosis (modified K-line − or within 4 mm) • Severe axial neck pain with CSM	Avoid in following: • >3 level disease • Congenital spinal stenosis • Dorsal pathology Specific complications: • Dysphagia • Longer operating time
Laminoplasty or laminectomy	• Multilevel compression • Lordosis (modified K-line +)	Avoid in following: • Instability and listhesis • Kyphosis (modified K-line—or within 4 mm) • Severe axial neck pain Specific complications: • Progression of kyphosis • Post-laminectomy membrane
Laminectomy and fusion	• Multilevel compression • Lordosis (modified K-line +) • Instability	Avoid in following: • Rigid kyphosis (modified K-line—or within 4 mm) Specific complications: • More blood loss • Longer hospitalization • More axial neck pain

Abbreviations: ACDF, anterior cervical diskectomy and fusion; CSM, cervical spondylotic myelopathy; OPLL, ossification of the posterior longitudinal ligament.

References

1. Angevine PD, McCormick PC. Posterior approach to cervical degenerative disease. In: Winn HR ed. Youmans Neurological Surgery. 6th ed. Elsevier; 2011, Vol. 3, 279;2868–2875
2. Lu Cw, Wang C, Ding MC, et al. posterior surgery may be the best option for the treatment of cervical spondylotic myelopathy: a comparative study in China. Int J Clin Exp Med 2018;11(10):10929–10939
3. Fehlings MG, Tetreault LA, Riew KD, et al. A clinical practice guideline for the management of patients with degenerative cervical myelopathy: recommendations for patients with mild, moderate, and severe disease and nonmyelopathic patients with evidence of cord compression. Global Spine J 2017;7(3, Suppl):70S–83S
4. Banerji D, Acharya R, Behari S, Chhabra DK, Jain VK. Corpectomy for multi-level cervical spondylosis and ossification of the posterior longitudinal ligament. Neurosurg Rev 1997;20(1):25–31
5. Parthiban J, Alves OL, Chandrachari KP, Ramani P, Zileli M. Value of surgery and nonsurgical approaches for cervical spondylotic myelopathy: WFNS Spine Committee Recommendations. Neurospine 2019;16(3):403–407
6. Karadimas SK, Erwin WM, Ely CG, Dettori JR, Fehlings MG. Pathophysiology and natural history of cervical spondylotic myelopathy. Spine 2013;38(22, Suppl 1):S21–S36
7. Shimokawa N, Sato H, Matsumoto H, Takami T. Review of radiological parameters, imaging characteristics, and their effect on optimal treatment approaches and surgical outcomes for cervical ossification of the posterior longitudinal ligament. Neurospine 2019;16(3):506–516
8. Gorter K. Influence of laminectomy on the course of cervical myelopathy. Acta Neurochir (Wien) 1976;33(3-4):265–281
9. Grieve JP, Kitchen ND, Moore AJ, Marsh HT. Results of posterior cervical foraminotomy for treatment of

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cervical spondylitic radiculopathy. Br J Neurosurg 2000;14(1):40–43
10. Matz PG, Anderson PA, Groff MW, et al; Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons. Cervical laminoplasty for the treatment of cervical degenerative myelopathy. J Neurosurg Spine 2009;11(2):157–169
11. Naderi S, Benzel EC, Baldwin NG. Cervical spondylotic myelopathy: surgical decision making. Neurosurg Focus 1996;1(6):e1
12. Yalamanchili PK, Vives MJ, Chaudhary SB. Cervical spondylotic myelopathy: factors in choosing the surgical approach. Adv Orthop 2012;2012:783762
13. Quinn JC, Kiely PD, Lebl DR, Hughes AP. Anterior surgical treatment of cervical spondylotic myelopathy: review article. HSSJ 2015;11(1):15–25
14. Kadoya S, Nakamura T, Kwak R. A microsurgical anterior osteophytectomy for cervical spondylotic myelopathy. Spine 1984;9(5):437–441
15. Patkar S. Advantages and disadvantages of the use of plate for anterior cervical fusion. In: Ramani P, Shoda M, Zileli M, Dohrmann G, eds. Surgical Management of Cervical Disc Herniation. Mumbai: Jaypee Medical Publishers (Pvt) Ltd.; 2012:91–97
16. Kahaer A, Chen R, Maitusong M, Mijiti P, Rexiti P. Zero-profile implant versus conventional cage-plate construct in anterior cervical discectomy and fusion for the treatment of single-level degenerative cervical spondylosis: a systematic review and meta-analysis. J Orthop Surg Res 2022;17(1):506
17. Matz PG, Holly LT, Mummaneni PV, et al; Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons. Anterior cervical surgery for the treatment of cervical degenerative myelopathy. J Neurosurg Spine 2009;11(2):170–173
18. Pojskic M, Saβ B, Nimsky C, Carl B. Application of an expandable cage for reconstruction of the cervical spine in a consecutive series of eighty-six patients. Medicina (Kaunas) 2020;56(12):642
19. Woiciechowsky C. Distractable vertebral cages for reconstruction after cervical corpectomy. Spine 2005;30(15):1736–1741
20. Fraser JF, Härtl R. Anterior approaches to fusion of the cervical spine: a metaanalysis of fusion rates. J Neurosurg Spine 2007;6(4):298–303
21. Vaccaro AR, Falatyn SP, Scuderi GJ, et al. Early failure of long segment anterior cervical plate fixation. J Spinal Disord 1998;11(5):410–415
22. Sasso RC, Ruggiero RA Jr, Reilly TM, Hall PV. Early reconstruction failures after multilevel cervical corpectomy. Spine 2003;28(2):140–142
23. Hussain M, Nassr A, Natarajan RN, An HS, Andersson GB. Biomechanical effects of anterior, posterior, and combined anterior-posterior instrumentation techniques on the stability of a multilevel cervical corpectomy construct: a finite element model analysis. Spine J 2011;11(4):324–330
24. Kumar GS, Rajshekhar V. Acute graft extrusion following central corpectomy in patients with cervical spondylotic myelopathy and ossified posterior longitudinal ligament. J Clin Neurosci 2009;16(3):373–377
25. Singh K, Vaccaro AR, Kim J, Lorenz EP, Lim TH, An HS. Enhancement of stability following anterior cervical corpectomy: a biomechanical study. Spine 2004;29(8):845–849
26. Dalbayrak S, Yilmaz M, Naderi S. "Skip" corpectomy in the treatment of multilevel cervical spondylotic myelopathy and ossified posterior longitudinal ligament. J Neurosurg Spine 2010; 12(1):33–38
27. Samuel AM, Moore HG, Vaishnav AS, et al. Effect of myelopathy on early clinical improvement after cervical disc replacement: a study of a local patient cohort and a large national cohort. Neurospine 2019;16(3):563–573
28. Lee JH, Lee YJ, Chang MC, Lee JH. Clinical effectiveness of artificial disc replacement in comparison with anterior cervical discectomy and fusion in the patients with cervical myelopathy: systematic review and meta-analysis. Neurospine 2023;20(3):1047–1060
29. Mohanty C, Massicotte EM, Fehlings MG, Shamji MF. Association of preoperative cervical spine alignment with spinal cord magnetic resonance imaging hyperintensity and myelopathy severity: analysis of a series of 124 cases. Spine 2015;40(1): 11–16
30. Nukala M, Abraham J, Khandige G, Shetty BK, Rao APA. Efficacy of diffusion tensor imaging in identification of degenerative cervical spondylotic myelopathy. Eur J Radiol Open 2018;6:16–23
31. Ghogawala Z, Terrin N, Dunbar MR, et al. Effect of ventral vs dorsal spinal surgery on patient-reported physical functioning in patients with

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cervical spondylotic myelopathy: a randomized clinical trial. JAMA 2021;325(10):942–951
32. Manzano GR, Casella G, Wang MY, Vanni S, Levi AD. A prospective, randomized trial comparing expansile cervical laminoplasty and cervical laminectomy and fusion for multilevel cervical myelopathy. Neurosurgery 2012;70(2):264–277
33. Cheung JPY, Cheung PWH, Chiu CK, Chan CYW, Kwan MK. Variations in practice among Asia-Pacific surgeons and recommendations for managing cervical myelopathy: the first Asia-Pacific Spine Society collaborative study. Asian Spine J 2019;13(1):45–55
34. Zhang L, Chen J, Cao C, et al. Anterior versus posterior approach for the therapy of multilevel cervical spondylotic myelopathy: a meta-analysis and systematic review. Arch Orthop Trauma Surg 2019;139(6):735–742
35. Shamji MF, Mohanty C, Massicotte EM, Fehlings MG. The association of cervical spine alignment with neurologic recovery in a prospective cohort of patients with surgical myelopathy: analysis of a series of 124 cases. World Neurosurg 2016; 86:112–119
36. El-Ghandour NMF, Soliman MAR, Ezzat AAM, Mohsen A, Zein-Elabedin M. The safety and efficacy of anterior versus posterior decompression surgery in degenerative cervical myelopathy: a prospective randomized trial. J Neurosurg Spine 2020;33(3):288–296
37. Nunna RS, Khalid S, Chiu RG, et al. Anterior vs posterior approach in multilevel cervical spondylotic myelopathy: a nationwide propensity-matched analysis of complications, outcomes, and narcotic use. Int J Spine Surg 2022;16(1):88–94
38. Wilkerson CG, Sherrod BA, Alvi MA, et al. Differences in patient-reported outcomes between anterior and posterior approaches for treatment of cervical spondylotic myelopathy: a quality outcomes database analysis. World Neurosurg 2022;160:e436–e441
39. Deora H, Kim SH, Behari S, et al; World Federation of Neurosurgical Societies (WFNS) Spine Committee. Anterior surgical techniques for cervical spondylotic myelopathy: WFNS Spine Committee recommendations. Neurospine 2019;16(3):408–420
40. Kwok SSS, Cheung JPY. Surgical decision-making for ossification of the posterior longitudinal ligament versus other types of degenerative cervical myelopathy: anterior versus posterior approaches. BMC Musculoskelet Disord 2020;21(1):823
41. Audat ZA, Fawareh MD, Radydeh AM, et al. Anterior versus posterior approach to treat cervical spondylotic myelopathy, clinical and radiological results with long period of follow-up. SAGE Open Med 2018;6:2050312118766199
42. Fehlings MG, Tetreault LA, Wilson JR, Skelly AC. Cervical spondylotic myelopathy: current state of the art and future directions. Spine 2013;38(22, Suppl 1):S1–S8
43. Ambati VS, Macki M, Chan AK, et al. Three-level ACDF versus 3-level laminectomy and fusion: are there differences in outcomes? An analysis of the Quality Outcomes Database cervical spondylotic myelopathy cohort. Neurosurg Focus 2023;55(3):E2

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24 Case of Anterior Third Ventricular Tumor

Shashwat Mishra and Hitesh Kumar

Introduction

The third ventricle is an uncommon site for occurrence of primary brain tumors. Only about 0.6 to 0.9% of all brain tumors are encountered in this location.[1] The surgical excision of third ventricular tumors is challenging owing to the deep location of the target, the narrow anatomical corridors of approach, and the need to protect critically important structures surrounding this region, which have very limited tolerance to surgical manipulation. However, often these tumors are pathologically benign and complete surgical excision offers a prospect of cure to the patient. Hence, the safe surgical resection of these lesions is of paramount importance.

The advancements in neuroimaging, endocrinological management, and neuroendoscopic techniques and neuronavigation have greatly aided surgeries performed in this region. Nevertheless, the success of the surgery still relies on anatomical knowledge and adherence to microsurgical principles.

Surgical Anatomy of the Anterior Third Ventricle

The third ventricle is traditionally described as funnel-shaped or slit-like cavity surrounded by important neurovascular structures such as the diencephalon, fornix, hypothalamus, pituitary stalk, optic chiasm, the pineal gland, and the venous structures belonging to the internal venous system (**Fig. 24.1**). It communicates with the lateral ventricles through the foramen of Monro and with the fourth ventricle via the aqueduct.

An arbitrary line drawn through the foramen of Monro to the aqueduct separates the anterior and posterior parts of the third ventricle.

Anatomical Boundaries of the Third Ventricle

The lamina terminalis forms the anterior wall of the third ventricle. It is a membrane composed of gray matter, pia mater, and ependyma, stretched between the optic chiasm inferiorly and the anterior commissure superiorly. It is thought to be devoid of functionally important neurons and is primarily constituted from paucicellular, fibrillar gliotic tissue.[2] It is the broadest face of the third ventricle. The arrow-shaped inferior attachment of the lamina

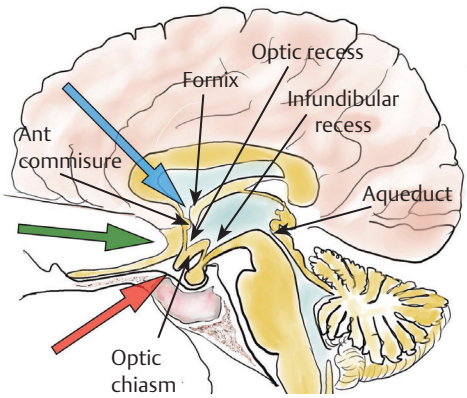

Fig. 24.1 Anatomical boundaries of the anterior third ventricle. Three principal surgical approaches to the anterior third ventricle are depicted: transventricular transforaminal (*blue arrow*), translamina terminalis (*green arrow*), and endoscopic endonasal (*red arrow*).

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terminalis with the optic chiasm encloses the chiasmal recess of the third ventricle. Surgical approaches through the lamina terminalis form one of the most frequent methods to access the anterior third ventricle.

Dorsally, the third ventricle cavity communicates with the lateral ventricles through the foramina of Monro. Hence, these foramina provide a natural corridor to reach the third ventricle with the approaches routed through the lateral ventricles.

It is important to be cognizant of the important anatomical relationships of the foramen of Monro to avoid inadvertent injury to the important neurovascular structures bordering it when surgical manipulations are being performed for removing third ventricular pathologies. The junction between the columns and body of fornix forms the anterior boundary of the foramina and the anterior pole of the thalamus borders it posteriorly. Notably, the corticobulbar fibers in the genu of the anterior capsule approach very close to the lateral border of the foramen of Monro sub-ependymally.

Normally, the foramina are crescent-shaped. However, they assume a more rounded configuration as the ventricular system dilates in patients with hydrocephalus.

The foramen of Monro and the lamina terminalis are the most frequent avenues of access to the third ventricle.

Roof of the Third Ventricle

The roof of the third ventricle is a four-layered structure. The superior most layer is formed by the segments of the fornix (the body anteriorly and the crura along with the hippocampal commissure posteriorly). The tela choroidea form the second and the fourth layers of the roof. The intervening space between the two layers of tela choroidea is occupied by the velum interpositum, which is composed of the branches of the medial posterior choroidal arteries and tributaries of the internal cerebral vein. The choroid plexus is attached to the fornix medially and the stria medullaris of the thalamus laterally by taenia fornicis and the taenia thalami respectively. Among the two taeniae, the forniceal attachment transmits relatively fewer vascular structures and hence is preferred for dissection.

Floor and Lateral Walls of the Third Ventricle

The floor of the third ventricle stretches between the optic chiasm anteriorly and the aqueduct posteriorly. From anterior to posterior, the structures encountered along the floor are as follows: the chiasm, infundibular recess, tuber cinereum, mammillary bodies, posterior perforated substance, tegmen of the midbrain, and aqueduct. Laterally, the walls are formed by the medial surface of the thalamus superiorly and the hypothalamus posteriorly. The thalamus and the hypothalamus are separated by the hypothalamic sulcus extending from the foramen of Monro to the aqueduct of Sylvius.

Associated Venous Structures and Choroid Plexus

The venous anatomy, especially that of the internal venous system, is of critical importance during the planning and execution of surgical approaches to the third ventricle. The thalamostriate vein is formed by the union of the anterior caudate vein and the vein of the stria thalami in the striothalamic sulcus, which separates the caudate tail and the thalamus. This vein can be identified as it crosses from the lateral to the medial side at the posterior margin of the foramen of Monro and is partially covered by the ependyma in its lateral course.

After traversing the foramen of Monro, the course thalamostriate vein makes a U-shaped turn posteriorly (venous angle) and becomes the internal cerebral vein (ICV). In

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almost two-thirds of cases, the venous angle lies at the posterior margin of the foramen of Monro, when it is called a "true venous angle." However, in up to a third, it may lie more posteriorly beyond the foraminal margin and is called the false venous angle. The anterior septal vein (ASV), traveling along the ependymal surface of the septum pellucidum medially, joins the venous angle or the ICV at a variable location. The location of the ASV–ICV junction and the configuration of the venous angle is of critical surgical importance. In case of a true venous angle with ASV–ICV junction close to the foramen of Monro, the ASV may need to be sacrificed to enlarge the foraminal opening posteriorly. However, ASV–ICV junction is situated posterior to the venous angle; it is possible to preserve the vein by skeletonizing its course through the taenia fornicis.

Normally, there is no venous communication between the bilateral ICVs and they can be separated avascularly in the midline.

Common Pathologies Encountered in the Third Ventricle

Table 24.1 lists the common pathologies seen in the third ventricle, their clinical presentation, and unique features. The imaging of most pathological lesions within the anterior third ventricle is sufficiently distinctive so that experienced radiologists can readily predict the pathological diagnosis with a fair degree of confidence.[3]

Case Description 1

A 16-year-old adolescent male presented to us with frequent episodes of frontal headache with dizziness and staring spells which had increased in frequency over the past 3 months before presentation. Imaging revealed a sub-centimetric lesion in the anterior third ventricle near the foramen of Monro (**Fig. 24.2a**) with imaging features suggestive of colloid cyst.

In view of the crescendo headaches and worsening symptoms, surgical excision of the cyst was offered to the patient. After obtaining informed consent, colloid cyst excision through anterior interhemispheric transcallosal approach was planned.

Operative Procedure

A linear scalp incision biased toward the right side was made parallel to the coronal suture (**Fig. 24.2b**). After placing burr holes in the midline and freeing the sagittal sinus extensively from the undersurface of the bone, a triangular craniotomy was made with its widest edge along the midline and about 5 cm long. The dural flap was elevated based on the sinus after careful observation of the course of the bridging veins. In this case, the venous anatomy was favorable; however, a modified dural opening may be needed in some cases, as depicted in **Fig. 24.2c**.

The interhemispheric fissure is dissected, with the branches of the pericallosal artery offering a useful guide to locating the plane of the fissure when the cingulate gyri are tightly adherent to each other. The corpus callosum is identified by its unmistakable white shiny appearance and overlying longitudinally oriented symmetrically running pericallosal arteries.

Following the callosotomy, once the ventricle is entered, the surgeon must orient toward the ventricular anatomy by following the choroid plexus anteriorly to its disappearance at the foramen of Monro. Medial to the choroid plexus we have the fornix inferiorly and the septum pellucidum superiorly. The veins of the lateral ventricle are seen lateral to the choroid plexus.

Once the previously discussed anatomical landmarks of the foramen of Monro are established, the distortion of the anatomy by the pathology dictates the further choice of

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Table 24.1 Commonly encountered lesions in the third ventricle

Lesion	Clinical presentation	Imaging features and unique characteristics
Pediatric age group		
1. Craniopharyngiomas	Visual loss, headache, hypopituitarism, diabetes insipidus	Calcified lesions on CT Heterogenous appearance on MRI with peripherally enhancing cystic solid lesions
2. Pilocytic astrocytoma (chiasmatic/ hypothalamic gliomas)	Visual field defects, neurocutaneous stigmata	Enhancing masses with spread along the optic pathways[4]
3. Langerhans cell histiocytosis	Diabetes insipidus	Young children (<2 years), loss of physiological pituitary bright spot (T1W MRI), thickening of the stalk and occasionally hypothalamic mass lesions
4. Hypothalamic hamartoma	Epilepsy, precocious puberty	Mass lesion arising from the floor of the third ventricle, nonenhancing
5. Germinoma	Diabetes insipidus without hypopituitarism	Hyperattenuating mass on CT with homogenous uniform enhancement in MRI; satellite lesions in pineal region and evidence of CSF spread
6. Colloid cysts	Similar to adult age group	
7. Choroid plexus papilloma/carcinoma	Enlarging head size, hydrocephalus	Frond like brilliantly enhancing mass, pedunculated surrounded by CSF, speckled calcification on CT[5]
Adult age group		
1. Colloid cysts	90% asymptomatic; symptoms: episodic/crescendo headache, dizziness, occasionally life-threatening extremis	Well-defined rounded lesion in anterior third ventricle, hyperdense on CT, iso- or hypointense on T2W MRI depending on thickness of cyst content[6]
2. Subependymoma	Symptoms consistent with chronic hydrocephalus (headache, ataxia, memory loss)	Hypointense on T1W MRI, hyperintense on T2W, nonenhancing on post Gd MRI
3. Choroid plexus papilloma	Hydrocephalus	Similar to that in pediatric age group
4. Craniopharyngoma	Visual loss, hypopituitarism	Similar to that in pediatric age group, however, solid lesions more common
5. Chordoid glioma	Rare lesion	Homogenous enhancement reminiscent of meningiomas

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; Gd MRI, gadolinium-based MRI; MRI, magnetic resonance imaging; T1W MRI, T1-weighted MRI; T2W MRi, T2-weighted MRI.

the operative corridor. The transforaminal corridor through the foramen of the Monro may provide sufficient room when the foramen is dilated. When the foramen needs expansion, the suprachoroidal route traversing the taenia fornicis is preferable (**Fig. 24.2d,e,f**). Alternatives include the transchoroidal corridor (involving the coagulation and division of the choroid plexus) or the sub-choroidal corridor (which requires the

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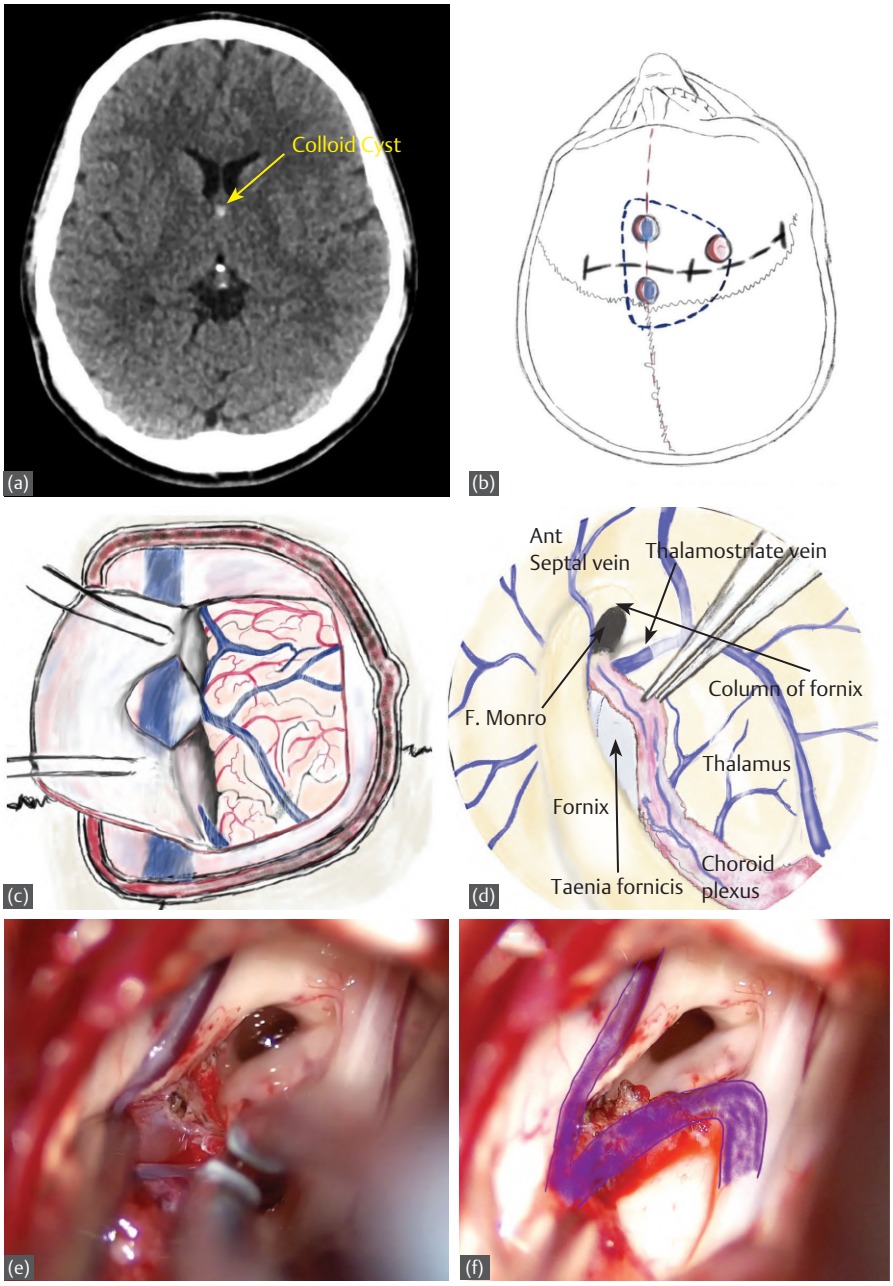

Fig. 24.2 **(a)** Plain CT of head showing a small colloid cyst at the foramen of Monro. **(b)** Linear incision and craniotomy. **(c)** Modified dural opening in case of unfavorable bridging vein anatomy. **(d)** A diagrammatic depiction of the anatomy around the foramen of Monro following transcallosal exposure (right lateral ventricle). **(e)** Colloid cyst visualized after posterior enlargement of the foraminal opening following division of the taenia fornicis. **(f)** Enhanced view of the anatomy after cyst excision showing the venous angle and course of the anterior septal vein.

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dissection of the taenia thalami and lateral mobilization of the choroid plexus).

In this case, since the cyst was not visible through the foramina, it was reached in the roof of the third ventricle after widening the foramina posteriorly through the supra-choroidal route.

The cyst was excised totally, and the patient made an unremarkable recovery.

Discussion

The anterior third ventricle tumors are approached primarily through the lamina terminalis or the transforaminal approach (via the foramen of Monro) and its modifications. The lamina terminalis approach offers the advantage of an extra-axial route up to the face of the lamina terminalis. The trans-foraminal corridor, on the other hand, necessarily requires a parenchymal incision and entry into the lateral ventricles. The interhemispheric transcallosal approach through the third ventricle effectively exploits the naturally available space of the interhemispheric fissure till the callosal incision. However, it suffers from the natural limitations of the narrowness of the corridor when used for lesions that have an epicenter into the third ventricle but extend into the frontal horn. A transcortical transventricular approach through the middle frontal gyrus is preferable in those cases.

The transcortical approaches have been frequently blamed for a higher incidence of postoperative seizures due to cortical violation. However, recent studies have questioned this notion and have found the incidence of seizures to be similar between the transcortical and transcallosal approaches.[7–9]

Endoscopically controlled colloid cyst excision has been gaining popularity with the rapid evolution in endoscopic technology and neurosurgical techniques. Recent reviews have still ascertained superior resection rates and lower recurrence rates in microsurgical cyst excision compared to endoscopic techniques. However, the rates of operative morbidity have been consistently lower with endoscopic cyst excision in recent studies.[10,11]

Endonasal endoscopic resection for craniopharyngiomas has rapidly gained favor with increasing experience in endoscopic skull base techniques and advances in the prevention/management of postoperative cerebrospinal fluid (CSF) leak, which is the most bothersome complication of endoscopic skull base surgery.

However, not all morphologies of craniopharyngioma are suitable for endoscopic excision, especially when the tumor is confined almost entirely to the third ventricle. The tubero-infundibular configuration of tumors[12,13] is most appropriate, as this subset separates the optic apparatus and hypophyseal structures upon growth, providing a suitable corridor for the endonasal endoscopic approach. Intra-third ventricular tumors, where the hypothalamus is displaced inferiorly below the tumor, are not ideal for an endoscopic approach. Tumors with significant lateral extension toward and beyond the Sylvian fissure are best suited for transcranial surgery.

Conclusion

Third ventricular lesions are challenging to manage surgically due to their deep location, intricate anatomy, and sensitivity of the surrounding structures to surgical manipulation. Effective surgical planning relies on detailed analysis of radiological images, where the pathological diagnosis of third ventricular lesions can be predicted with a high degree of confidence based on their characteristic appearance. The execution of the surgical plan needs a deep understanding of the third ventricular surgical anatomy and meticulous microsurgical/endoscopic techniques for optimal outcomes.

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References

1. Chibbaro S, Di Rocco F, Makiese O, et al. Neuroendoscopic management of posterior third ventricle and pineal region tumors: technique, limitation, and possible complication avoidance. Neurosurg Rev 2012;35(3):331–338, discussion 338–340
2. Tubbs RS, Nguyen HS, Loukas M, Cohen-Gadol AA. Anatomic study of the lamina terminalis: neurosurgical relevance in approaching lesions within and around the third ventricle. Childs Nerv Syst 2012;28(8):1149–1156
3. Glastonbury CM, Osborn AG, Salzman KL. Masses and malformations of the third ventricle: normal anatomic relationships and differential diagnoses. Radiographics 2011;31(7):1889–1905
4. Goncalves FG, Mahecha-Carvajal ME, Desa A, et al. Imaging of supratentorial intraventricular masses in children: a pictorial review—part 2. Neuroradiology 2024;66(5):699–716
5. Gonçalves FG, Mahecha-Carvajal ME, Desa A, et al. Imaging of supratentorial intraventricular masses in children: a pictorial review—part 1. Neuroradiology 2024;66(5):677–698
6. Khanpara SD, Day AL, Bhattacharjee MB, Riascos RF, Fernelius JP, Westmark KD. The variable appearance of third ventricular colloid cysts: correlation with histopathology and the risk of obstructive ventriculomegaly. AJNR Am J Neuroradiol 2020;41(10):1833–1840
7. Milligan BD, Meyer FB. Morbidity of transcallosal and transcortical approaches to lesions in and around the lateral and third ventricles: a single-institution experience. Neurosurgery 2010; 67(6):1483–1496, discussion 1496
8. Desai KI, Nadkarni TD, Muzumdar DP, Goel AH. Surgical management of colloid cyst of the third ventricle—a study of 105 cases. Surg Neurol 2002;57(5):295–302, discussion 302–304
9. Kasowski H, Piepmeier JM. Transcallosal approach for tumors of the lateral and third ventricles. Neurosurg Focus 2001;10(6):E3
10. Sheikh AB, Mendelson ZS, Liu JK. Endoscopic versus microsurgical resection of colloid cysts: a systematic review and meta-analysis of 1,278 patients. World Neurosurg 2014;82(6):1187–1197
11. Sethi A, Cavalcante D, Ormond DR. Endoscopic versus microscopic transcallosal excision of colloid cysts: a systematic review in the era of complete endoscopic excision. World Neurosurg 2019;132:e53–e58
12. Zoli M, Guaraldi F, Zenesini C, et al. Role of endoscopic endonasal approach for craniopharyngiomas extending into the third ventricle in adults. Brain Spine 2022;2:100910
13. Prieto R, Pascual JM, Rosdolsky M, Barrios L. Preoperative assessment of craniopharyngioma adherence: magnetic resonance imaging findings correlated with the severity of tumor attachment to the hypothalamus. World Neurosurg 2018; 110:e404–e426

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25 Trigeminal Neuralgia: Current Understanding and Management Review

Amol Mittal and Adesh Shrivastava

Introduction and Epidemiology

Trigeminal neuralgia (TN) is a severely debilitating and agonizing chronic pain condition characterized by sudden, intense, and electric shock-like pain episodes affecting the distribution of the trigeminal nerve precipitated by innocuous stimuli. Although the modern medical understanding of this condition has evolved significantly over the centuries, accounts of its characteristic symptoms can be traced back in history, indicating that this affliction has been recognized and documented by clinicians throughout history, viz., Hippocrates, Aretaeus of Cappadocia, Avicenna, Johannes Fehr, Elias Schmidt, John Locke, and John Fothergill. In 1756, Nicholas Andre coined the term tic douloureux, referring to the pain's sharp, shooting, lancinating quality and facial grimaces.[1] The annual incidence of TN varies from 4.3 to 26.8 per 100,000 people and is approximately 45 per 100,000 in individuals aged >80 years.[2] Various risk factors have been identified for TN such as multiple sclerosis and hypertension. Nearly 2% of the patients with Multiple Sclerosis (MS) suffer from TN and TN can precede the diagnosis of MS in 15% of the cases.[3,4]

Diagnosis and Classification

The diagnosis of TN is mainly historical. Often the patient vividly remembers the first pain episode. Although several diagnostic classifications exist, three are most commonly used, viz., International Association for the Study of Pain (IASP), the ICHD-3, and the Burchiel classification of facial pain.[5–7] The Burchiel system classifies the TN based on the patient's history and is vital from a neurosurgery perspective. It includes facial pain of spontaneous onset viz TN type 1 (>50% episodic pain), TN type 2 (constant dull aching pain); due to trigeminal injury viz neuropathic pain, deafferentation pain, symptomatic TN, post-herpetic neuralgia; and lastly, somatoform pan disorder which includes atypical facial pain. The classic TN type 1 pain is located in V2/V3 segments (less commonly in V1 segments), unilateral, excruciating, nonradiating, sudden spontaneous in onset lasting from a few seconds to a maximum of 2 minutes, shooting or stabbing in character, aggravated by washing, shaving, drinking, eating or chewing, cold wind, and relieves on its own with intervening pain-free interval. The associated symptoms include sensory changes and the presence of trigger zones.[8] The Burchiel system classifies TN into types 1 and 2 based on dominant pain phenotype whereas IASP/ICHD-3 distinguishes classical from idiopathic in the presence/absence of neurovascular conflict and type 2 constant, dull-aching pain.[5–7]

In one prospective study, it has been observed that in patients with TN, in addition to pain paroxysm, there is the presence of continuous pain in more than half of the cases and autonomic and sensory abnormalities in nearly one-third of the cases.[9]

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Diagnostic Tests

The diagnosis is based mainly on the patient's history. The causative factor for TN is unknown. However, the presence of neurovascular compression (NVC) is often associated with TN. Nevertheless, the TN can occur in the absence of the neurovascular conflict. The imaging modality of choice is MRI of brain with CISS/FIESTA sequences which provide evidence of any possible neurovascular conflict if present. Additionally, MR angiography provides accurate evidence of arterial vasculature surrounding the trigeminal nerve. The CISS and MR angiography can be merged to see the possible neurovascular conflict during the preoperative planning for the microvascular decompression (MVD).[10] The sensitivity for detecting NVC ranges from 96 to 97%.[11,12] The more severe the NVC and resulting nerve distortion seen on preoperative imaging, the more likely the patient will experience a favorable outcome from surgical decompression of the trigeminal nerve.[13,14] The usage of diffusion tensor imaging (DTI) has also been supported by few studies in patients with TN. The pattern of radial diffusivity and the apparent diffusion coefficient (ADC) were significantly elevated in patients with type 1 TN than in type 2 and the ultrastructural changes seen have been corroborated with radial diffusivity.[15,16] The DTI has also been utilized to predict pain relief after stereotactic radiosurgery (SRS), MVD, and radiofrequency (RF) ablation. In patients who underwent SRS for TN, those with pain resolution after SRS exhibited a significantly lower fractional anisotropy (FA) value on the affected side.[17] In addition, the TN is dramatically relieved by the use of voltage-gated sodium channel blockers, which also reinforces the diagnosis of the TN. The antiepileptic drug (AED) serves diagnostic and therapeutic purposes in TN. Clinical examination may be unremarkable in patients with TN. However, studies have shown that there may be mild deficits upon sensitive testing including quantitative sensory testing, warm and cold detection, elevated tactile sensations, hypoesthesia etc.[18]

Differential Diagnosis

Various etiologies have been identified for facial pain that includes multiple sclerosis, trauma, iatrogenic injury, post-herpetic neuralgia, trigeminal deafferentation pain, trigeminal neuropathic pain, odontogenic causes, temporomandibular joint diseases, giant cell arteritis, burning mouth syndrome, unilateral neuralgia with autonomic features, and conjunctival injection short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) attack/short-lasting unilateral neuralgiform headache attack (SUNA) etc. TN has to be differentiated from the above due to its spontaneous nature, episodic pain, and unilateral character.

Pathophysiology

- Compression of the trigeminal nerve complex containing central myelin by an artery or vein. The more severe the NVC and resulting nerve distortion seen on preoperative imaging, the more likely the patient will experience a favorable outcome from surgical decompression of the trigeminal nerve further reinforcing the above notion.[13,14] The demyelinating changes are reversible if decompression is done early.[19,20]
- The ignition hypothesis proposed by Devor suggested that the injury to the trigeminal nerve due to NVC makes the demyelinated axons hyperexcitable as a result of synchronized after-discharge activity. In addition, it has been observed that TN trigger zone activation may involve amplification and cross-excitation of discharges from myelinated to nonmyelinated afferents (epiphatic transmission).[15,21]
- Involvement of voltage-gated sodium channels causing aberrant

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electrophysiology. It has been noted in patients with TN that the expression of Nav 1.3 and Nav 1.7 are upregulated and downregulated, respectively.[22] Carbamazepine (CBZ) has been noted to normalize the activity associated with VGSC Nav 1.3/1.7.[23,24]

- The symptoms of TN may occur without the typical precipitating injury associated with NVC. Electrophysiological studies indicate broader involvement of trigeminal sensory pathways, with functional derangements in the spinal trigeminal nucleus. Quantitative measures of trigeminal nociceptive transmission, such as nociceptive blink reflex and pain-related evoked potentials, can differentiate between classical TN and persistent pain, potentially reflecting supraspinal adaptations in chronic pain. Neuroimaging studies further demonstrate complex brain alterations in regions associated with the "pain matrix," including structural, functional, and white matter changes. Collectively, these findings indicate that craniofacial pain in TN may be qualitatively distinct from somatic nociception, with a tendency toward sensitization and greater limbic system involvement.[25–27]
- TN usually affects the elderly. It is more common in females. With age, the cisternal arteries elongate and therefore the chances of neurovascular conflict are higher in the elderly. In addition, the posterior fossa in females is smaller compared to males highlighting the occurrence of TN in older individuals and more commonly in females.[10,28]

Management

Pharmacologic

More than 90% of the patients with TN respond favorably to the usage of voltage-gated sodium channel blockers.[29] The level of present evidence is low but the treatment efficacy is good.[30] The response rate is similar with CBZ and oxcarbamazepine. However, the latter results in few drug interactions.[31] The incidence of hyponatremia ranges from 8 to 22% with CBZ and oxcarbamazepine.[32] Other antiepileptic drug therapy includes the usage of phenytoin, lamotrigine, and gabapentin. The usage of lamotrigine is advocated as monotherapy as a second-line drug in patients who can't tolerate CBZ.[33] Several studies have shown a similar efficacy of phenytoin compared with CBZ. However, no direct comparison is available in the literature.[34] The usage of gabapentin/GABA agonist in TN has also been effective in controlling neuropathic pain. However, the present evidence is weak although the side effects are less compared with CBZ.[30] Recently, various non-AEDs have been utilized in the management of TN, viz., baclofen, tizanidine, and sumatriptans. However, a recent Cochrane review failed to draw any definitive conclusions about the usage of these drugs in TN.[35] For acute TN, strategies include local anesthetics (topical, intravenous, local), intravenous phenytoin infusion, and sumatriptan.[36] In patients with type 2 TN or TN with consistent pain, observational studies suggest lower response rates to CBZ/OXC and poorer surgical outcomes. Medical treatment is largely guided by analogy to other neuropathic conditions, with first-line therapies including pregabalin, gabapentin, tricyclic antidepressants, calcium channel blockers, and selective serotonin-reuptake inhibitors. Similar treatment strategies are used for symptomatic or secondary TN including multiple sclerosis.[37]

It is noted that nearly 25% of the patients will report adverse reactions over 1 year and in the next 2 to 6 years approximately 5% of patients will report an increase in the pain severity or duration. In addition, it has been noted that with time the symptoms of classical TN may progress to TN type 2—dull continuous aching pain—if left untreated.[38]

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Percutaneous

The percutaneous treatment of TN was first reported by Patruban in 1853.[39] Later, in early 1900's, Hartel used a similar anterior approach currently practiced for injecting the alcohol.[40] The RF lesioning was introduced in 1960 by Sweet and it was employed for TN in 1974.[41] Balloon compression (BC) causing internal neurolysis of the trigeminal nerve was introduced in 1983 by Mullan and Lichtor.[42] For percutaneous procedures, the retrogasserian area or the triangular plexus has been identified as the ideal lesioning site for TN.[43]

The common indications for percutaneous procedures include medically unfit patients with severe comorbidities, recurrent TN after MVD, and TN patients with multiple sclerosis, pontine infarction, and brain stem demyelinating disorders. For patients with TN and MS, careful planning needs to be done and the patient should be prognosticated adequately. Even in cases where a neurovascular conflict is observed in MS, these patients are unlikely to get any benefit from the surgery owing to the central demyelination.[44] The surgical armamentarium for percutaneous procedures include the following: thermocoagulation using RF ablation, glycerol rhizotomy (GR), and BC. All percutaneous procedures are classified as ablative procedures, involving the insertion of a needle, RF electrode, or balloon into the Meckel cave via the foramen ovale. The end result is immediate pain relief, but it may come with the expense of facial numbness. In some cases, there may be facial dysesthetic pain and masseter weakness.

For percutaneous procedures, RF rhizotomy has been found to offer the highest success rate in relieving TN pain. Some reports have shown its outcomes to be comparable to those of MVD. Long-term pain relief has been observed in up to 75% of patients undergoing RF rhizotomy. Additionally, glycerol rhizotomy has demonstrated pain improvement in 55% of patients, while BC has been associated with a 73% rate of pain relief at a 4-year follow-up.[45] Currently, there is no Class 1 evidence available to directly compare these percutaneous procedures. However, a recent meta-analysis compared the safety and efficacy of these three techniques. RF showed not only significantly higher odds of immediate pain relief compared to ganglion radiofrequency (GR), but also a higher risk of anesthesia and a lower risk of herpes eruption. BC had a significantly higher risk of mastication weakness and diplopia compared to GR. There were no significant differences between BC and RF. Overall, RF seems to provide better immediate pain relief than GR, but all three techniques can have associated complications.[46] In cases of TN related to multiple sclerosis, BC provides the highest pain relief response and a longer duration of pain-free periods compared to gamma knife, GR, RF, and MVD.[47]

The immediate pain relief provided by percutaneous procedures is often accompanied by corneal hypoesthesia, facial dysthetic pain, and motor weakness, particularly in the masseter muscle. Facial dysthetic pain is typical with all three methods (RF 6–9%, GR 4%, BC 5%). However, masseter weakness is more frequently associated with BC.[45,48]

Stereotactic Radiosurgery

Lars Leksell first introduced the concept of using radiosurgery to treat facial pain. He used an ortho-voltage stereotactic technique to treat TN.[49]

The success of pain relief and the pain-free interval after SRS is more effective when used as a primary treatment rather than as a rescue therapy.[50,51] Overall all second-line treatments for recurrent MVD carries a lower success rate and lower pain relief. Previous surgical exploration hinders optimized target selection for radiosurgery as it distorts the cisternal anatomy and causes scarring and fibrosis. The success of SRS depends on the type of TN (typical/atypical), absence of any prior surgical intervention, presence of a

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neurovascular conflict, and greater irradiation of the trigeminal nerve.[52,53]

The target for SRS is the root entry zone along with the cisternal segment of the trigeminal nerve with a single isocenter. However, in the case of the short cisternal segment, beam blocking or beam reshaping may be required to avoid excess brain stem radiation exposure.

The trigeminal nerve can be targeted via SRS proximally or more anteriorly. A more anterior target results in good pain relief, and less brain stem radiation toxicity compared with the target at the root entry zone, which provides more robust pain relief at the expense of increased radiation toxicity to the brain stem and increased facial numbness.[54–56] In addition, a single, 4-mm isocenter collimator is advisable for using gamma knife radiosurgery (GKRS) for TN.[57] The dosage ranges from 70 to 90 Gy.[58] With dosage toward the higher gradient, the isocenter should be away from the brain stem. In addition, the integral dose of between 1.4 and 2.7 mJ offers good pain relief and a higher dosage is associated with facial numbness.[59]

The initial latency period from the SRS to pain relief ranges from 10 days to 4 weeks.[50,52,60,61] The incidence of pain relief after GKRS is 83% after 12 months, which decreases to 55% at 5 years.[62,63] The most common complication after SRS is delayed pain relief, and facial numbness in up to one-fifth of the patients with associated pain in 10% of them.[64]

The more the proximal site of lesioning the more is the incidence of facial numbness.

For TN associated with MS, SRS has shown promising results. Rogers et al noted 80% pain relief in their series of 15 patients at 17 months follow-up with a dose range of between 70 and 90 Gy. The International Gamma Knife Consortium reported nearly one-third of cases (n = 236) achieved complete pain relief whereas nearly 88% had reasonable pain relief at 14 months follow-up.[65,66]

Microvascular Decompression

NVC causing TN was first explained by Walter E. Dandy in 1934. However, the first decompression was performed by James Gardner in 1959 and was successfully popularized by Peter Jannetta.[68,69] From the patient's perspective, the satisfaction rate was much higher with MVD compared to medical treatment.[70] The indications for the MVD include failure of medical therapy for at least 1 year or development of side effects at 4 to 6 times the standard basic dosage (200 mg/d for CBZ, 300 mg/d for OXC)[30,71] and young patients with type 1 TN.

MVD offers the most pain relief and lowest recurrence compared with any surgical intervention.[72] Patients with MS should ideally be offered ablative procedures due to high incidences of recurrence among this cohort. Few studies have shown that in patients with MS or without neurovascular conflict, open rhizotomy is effective in controlling the symptoms.[73,74] The long-term results of MVD are promising with multiple studies showing approximately 65% of the patients being completely pain-free at 10 and 20 years.[69,75] Patients with type 1 TN typically respond better. However, even for type 2 TN, MVD offers the best chance of pain relief compared with the other modalities. Arterial compression fares a better prognosis than venous compression due to regrowth of veins. Prolonged symptoms over the years, venous compression, and female gender increase the chances of recurrence after MVD.[69,76,77]

Stereotactic Radiosurgery or MVD?

MVD is a nonablative procedure that offers immediate pain relief and the durability of pain relief extends over many years. Multiple studies have shown that approximately 70% of patients are pain-free at 10 years.[78,79] Young patients with type 1 TN are the most suitable candidates for MVD. Any direct evidence

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comparing SRS and MVD is lacking. However, few studies have shown promising results as approximately 70% of the patients are pain-free at 5 years.[60] The major drawback of radiosurgery is the latency period for pain relief, facial numbness, and a higher rate of pain recurrence.[77] Radiosurgery can be considered in patients who are medically unfit for surgery, in the absence of any NVC, in the elderly population, and in case of failure of index MVD procedures, as repeat MVD carries higher complication risk.[69] Alternatively, in cases with failed primary SRS, a rescue MVD can be planned.

Recurrent TN

In cases where initial MVD fails to relieve symptoms, a redo-MVD can be successful in providing relief by identifying new conflict sites, such as compression of motor roots. Thorough exploration of both sensory and motor roots is crucial for successful MVD, and early reoperation for resistant TN does not increase complications.[80] Few studies have highlighted that a repeat MVD is unlikely to be effective unless vein compression is the cause.[81,82] For recurrent cases, glycerol or RF rhizotomy is recommended.[83] However, repeat glycerol injection carries a higher technical failure risk due to trigeminal cistern scarring, so RF rhizotomy may be preferable in such cases.[84] There is no evidence of greater technical failure with repeated RF or BC procedures.[45] The pain recurrence post radiosurgery ranges from 5 to 43%. The patients can be considered for repeat radiosurgery based on the initial response to radiosurgery. However, the incidence of facial numbness is higher than the index SRS.[60] The overall pain relief after the second sitting ranges from 72 to 85%. Additionally, it should be noted that the cumulative dose for an individual should range between 120 and 170 Gy.[85]

Conclusion

Gamma knife therapy has a longer interval to pain relief compared to other modalities, and its overall effectiveness and duration of pain relief are lower than MVD. However, pain relief achieved with gamma knife is more durable than with percutaneous procedures.[86-89] Although initial pain-free outcomes are similar between percutaneous procedures and MVD, the duration of pain relief is longer with MVD. Additionally, MVD has a lower incidence of side effects like hypesthesia, but higher rates of major complications and perioperative morbidity.[90-91]

The current evidence regarding the management of TN is of low to moderate quality. Medical management is the first line of treatment. However, adverse events limit its usability. Surgical treatment offers the longest and most durable pain relief. Given the evidence, patients with TN should consider the management decision based on multidisciplinary input.

References

1. Pearce JMS. Trigeminal neuralgia (Fothergill's disease) in the 17th and 18th centuries. J Neurol Neurosurg Psychiatry 2003;74(12):1688–1688
2. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol 1990;27(1):89–95
3. Pan S-L, Yen M-F, Chiu Y-H, Chen L-S, Chen H-H. Increased risk of trigeminal neuralgia after hypertension: a population-based study. Neurology 2011;77(17):1605–1610
4. Godazandeh K, Martinez Sosa S, Wu J, Zakrzewska JM. Trigeminal neuralgia: Comparison of characteristics and impact in patients with or without multiple sclerosis. Mult Scler Relat Disord 2019;34:41–46
5. Cruccu G, Finnerup NB, Jensen TS, et al. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. Neurology 2016;87(2):220–228

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6. Gobel H. 13. Painful lesions of the cranial nerves and other facial pain [Internet]. ICHD-3. Accessed July 31, 2024 at: https://ichd-3.org/13-painful-cranial-neuropathies-and-other-facial-pains/
7. Eller JL, Raslan AM, Burchiel KJ. Trigeminal neuralgia: definition and classification. Neurosurg Focus 2005;18(5):1-3. https://doi.org/10.3171/foc.2005.18.5.4
8. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia—a prospective systematic study of clinical characteristics in 158 patients. Headache 2014;54(10):1574–1582
9. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Concomitant persistent pain in classical trigeminal neuralgia—evidence for different subtypes. Headache 2014;54(7):1173–1183
10. Miller JP, Acar F, Hamilton BE, Burchiel KJ. Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia. J Neurosurg 2009;110(4):627–632
11. Lee A, McCartney S, Burbidge C, Raslan AM, Burchiel KJ. Trigeminal neuralgia occurs and recurs in the absence of neurovascular compression. J Neurosurg 2014;120(5):1048–1054
12. Leal PRL, Hermier M, Souza MA, Cristino-Filho G, Froment JC, Sindou M. Visualization of vascular compression of the trigeminal nerve with high-resolution 3T MRI: a prospective study comparing preoperative imaging analysis to surgical findings in 40 consecutive patients who underwent microvascular decompression for trigeminal neuralgia. Neurosurgery 2011;69(1):15–25, discussion 26
13. Hughes MA, Jani RH, Fakhran S, et al. Significance of degree of neurovascular compression in surgery for trigeminal neuralgia. J Neurosurg 2019;133(2):411–416
14. Panczykowski DM, Jani RH, Hughes MA, Sekula RF. Development and evaluation of a preoperative trigeminal neuralgia scoring system to predict long-term outcome following microvascular decompression. Neurosurgery 2020;87(1):71–79
15. Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. J Neurosurg 2002;96(3):532–543
16. Willsey MS, Collins KL, Conrad EC, Chubb HA, Patil PG. Diffusion tensor imaging reveals microstructural differences between subtypes of trigeminal neuralgia. J Neurosurg 2019;133(2):573–579
17. Tohyama S, Hung PS, Zhong J, Hodaie M. Early postsurgical diffusivity metrics for prognostication of long-term pain relief after Gamma Knife radiosurgery for trigeminal neuralgia. J Neurosurg 2018;131(2):539–548
18. Younis S, Maarbjerg S, Reimer M, et al. Quantitative sensory testing in classical trigeminal neuralgia—a blinded study in patients with and without concomitant persistent pain. Pain 2016;157(7):1407–1414
19. Miles JB, Eldridge PR, Haggett CE, Bowsher D. Sensory effects of microvascular decompression in trigeminal neuralgia. J Neurosurg 1997;86(2):193–196
20. Leal PRL, Roch J, Hermier M, Berthezene Y, Sindou M. Diffusion tensor imaging abnormalities of the trigeminal nerve root in patients with classical trigeminal neuralgia: a pre- and postoperative comparative study 4 years after microvascular decompression. Acta Neurochir (Wien) 2019;161(7):1415–1425
21. Burchiel KJ. Abnormal impulse generation in focally demyelinated trigeminal roots. J Neurosurg 1980;53(5):674–683
22. Siqueira SRDT, Alves B, Malpartida HMG, Teixeira MJ, Siqueira JTT. Abnormal expression of voltage-gated sodium channels Nav1.7, Nav1.3 and Nav1.8 in trigeminal neuralgia. Neuroscience 2009;164(2):573–577
23. Sun GC, Werkman TR, Battefeld A, Clare JJ, Wadman WJ. Carbamazepine and topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the Na(v)1.3 α-subunit. Epilepsia 2007;48(4):774–782
24. Adi T, Estacion M, Schulman BR, Vernino S, Dib-Hajj SD, Waxman SG. A novel gain-of-function Nav1.7 mutation in a carbamazepine-responsive patient with adult-onset painful peripheral neuropathy. Mol Pain 2018;14:1744806918815007
25. Rodriguez E, Sakurai K, Xu J, et al. A craniofacial-specific monosynaptic circuit enables heightened affective pain. Nat Neurosci 2017;20(12):1734–1743
26. Obermann M, Yoon M-S, Ese D, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. Neurology 2007;69(9):835–841

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27. Dubner R, Sharav Y, Gracely RH, Price DD. Idiopathic trigeminal neuralgia: sensory features and pain mechanisms. Pain 1987;31(1):23–33
28. Hardaway FA, Holste K, Ozturk G, et al. Sex-dependent posterior fossa anatomical differences in trigeminal neuralgia patients with and without neurovascular compression: a volumetric MRI age- and sex-matched case-control study. J Neurosurg 2019;132(2):631–638
29. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. J Headache Pain 2014;15(1):34
30. Cruccu G, Gronseth G, Alksne J, et al; American Academy of Neurology Society; European Federation of Neurological Society. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008;15(10):1013–1028
31. Baruzzi A, Albani F, Riva R. Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. Epilepsia 1994;35(Suppl 3):S14–S19
32. Berghuis B, van der Palen J, de Haan GJ, Lindhout D, Koeleman BPC, Sander JW; EpiPGX Consortium. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia 2017;58(7):1227–1233
33. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens LE. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997;73(2):223–230
34. Keppel Hesselink JM, Schatman ME. Phenytoin and carbamazepine in trigeminal neuralgia: marketing-based versus evidence-based treatment. J Pain Res 2017;10:1663–1666
35. Zhang J, Yang M, Zhou M, He L, Chen N, Zakrzewska JM. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database Syst Rev [Internet] 2013. Accessed August 1, 2024 at: https://doi.wiley.com/10.1002/14651858.CD004029.pub4
36. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. Br J Anaesth 2019;123(2):e385–e396
37. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14(2):162–173
38. Burchiel KJ, Slavin KV. On the natural history of trigeminal neuralgia. Neurosurgery 2000; 46(1):152–154, discussion 154–155
39. Harris W. A history of the treatment of trigeminal neuralgia. Postgrad Med J 1951;27(303):18–21
40. Hartel F. Ueber die intracranielle Injectionsbehandlung der Trigeminusneuralgie. Med Klin 1912;10:582–584. https://cir.nii.ac.jp/crid/1573105974509176704
41. Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. J Neurosurg 1974;40(2):143–156
42. Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. J Neurosurg 1983;59(6):1007–1012
43. Sindou M, Keravel Y. [Trigeminal neuralgia. Percutaneous thermocoagulation of the trigeminal nerve (author's transl)]. Neurochirurgie 1979; 25(3):166–172
44. Ariai MS, Mallory GW, Pollock BE. Outcomes after microvascular decompression for patients with trigeminal neuralgia and suspected multiple sclerosis. World Neurosurg 2014;81(3-4):599–603
45. Taha J. Trigeminal neuralgia: percutaneous procedures. Semin Neurosurg 2004;15:115–134
46. Texakalidis P, Xenos D, Tora MS, Wetzel JS, Boulis NM. Comparative safety and efficacy of percutaneous approaches for the treatment of trigeminal neuralgia: a systematic review and meta-analysis. Clin Neurol Neurosurg 2019;182:112–122
47. Mohammad-Mohammadi A, Recinos PF, Lee JH, Elson P, Barnett GH. Surgical outcomes of trigeminal neuralgia in patients with multiple sclerosis. Neurosurgery 2013;73(6):941–950, discussion 950
48. Tew JM, Morgan CJ, Grande AW. Percutaneous stereotactic rhizotomy in the treatment of intractable facial pain [Internet]. In: Schmidek and Sweet Operative Neurosurgical Techniques. Elsevier; 2012:1409–1418. Accessed August 1, 2024 at: https://linkinghub.elsevier.com/retrieve/pii/B9781416068396101248
49. Mathiesen T. Brain fragments—daily notes and reminiscences by Lars Leksell. Translated by Dan Leksell: Ekerlids Forlag; 2022, ISBN: 978–91–86,323–53–7. Acta Neurochir (Wien) 2022;164:2535–2536
50. Régis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F. Prospective controlled trial of gamma

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knife surgery for essential trigeminal neuralgia. J Neurosurg 2006;104(6):913–924
51. Maesawa S, Salame C, Flickinger JC, Pirris S, Kondziolka D, Lunsford LD. Clinical outcomes after stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2001;94(1):14–20
52. Pollock BE, Phuong LK, Gorman DA, Foote RL, Stafford SL. Stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2002;97(2): 347–353
53. Brisman R, Khandji AG, Mooij RBM. Trigeminal nerve-blood vessel relationship as revealed by high-resolution magnetic resonance imaging and its effect on pain relief after gamma knife radiosurgery for trigeminal neuralgia. Neurosurgery 2002;50(6):1261–1266, discussion 1266–1267
54. Xu Z, Schlesinger D, Moldovan K, et al. Impact of target location on the response of trigeminal neuralgia to stereotactic radiosurgery. J Neurosurg 2014;120(3):716–724
55. Massager N, Lorenzoni J, Devriendt D, Desmedt F, Brotchi J, Levivier M. Gamma knife surgery for idiopathic trigeminal neuralgia performed using a far-anterior cisternal target and a high dose of radiation. J Neurosurg 2004;100(4):597–605
56. Régis J, Bartolomei F, Metellus P, et al. Radiosurgery for trigeminal neuralgia and epilepsy. Neurosurg Clin N Am 1999;10(2):359–377
57. Kanner AA, Neyman G, Suh JH, Weinhous MS, Lee S-Y, Barnett GH. Gamma knife radiosurgery for trigeminal neuralgia: comparing the use of a 4-mm versus concentric 4- and 8-mm collimators. Stereotact Funct Neurosurg 2004;82(1):49–57
58. Tawk RG, Duffy-Fronckowiak M, Scott BE, et al. Stereotactic gamma knife surgery for trigeminal neuralgia: detailed analysis of treatment response. J Neurosurg 2005;102(3):442–449
59. Mousavi SH, Niranjan A, Akpinar B, et al. A proposed plan for personalized radiosurgery in patients with trigeminal neuralgia. J Neurosurg 2018;128(2):452–459
60. Kondziolka D, Zorro O, Lobato-Polo J, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2010;112(4): 758–765
61. Fountas KN, Smith JR, Lee GP, Jenkins PD, Cantrell RR, Sheils WC. Gamma Knife stereotactic radiosurgical treatment of idiopathic trigeminal neuralgia: long-term outcome and complications. Neurosurg Focus 2007;23(6):E8
62. Dellaretti M, Reyns N, Touzet G, et al. Clinical outcomes after Gamma Knife surgery for idiopathic trigeminal neuralgia: review of 76 consecutive cases. J Neurosurg 2008;109(Suppl):173–178
63. Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for the treatment of trigeminal neuralgia. Clin J Pain 2002;18(1):42–47
64. Little AS, Shetter AG, Shetter ME, Bay C, Rogers CL. Long-term pain response and quality of life in patients with typical trigeminal neuralgia treated with gamma knife stereotactic radiosurgery. Neurosurgery 2008;63(5):915–923, discussion 923–924
65. Rogers CL, Shetter AG, Ponce FA, Fiedler JA, Smith KA, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia associated with multiple sclerosis. J Neurosurg 2002;97(5, Suppl):529–532
66. Xu Z, Mathieu D, Heroux F, et al. Stereotactic radiosurgery for trigeminal neuralgia in patients with multiple sclerosis: a multicenter study. Neurosurgery 2019;84(2):499–505
67. Dandy, W.E. (1934). Concerning the cause of trigeminal neuralgia. American Journal of Surgery, 24, 447-455.
68. Gardner WJ. Concerning the mechanism of trigeminal neuralgia and hemifacial spasm. J Neurosurg 1962;19:947–958
69. Barker FG II, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 1996;334(17):1077–1083
70. Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. Pain 2007;131(3):302–310
71. Besi E, Boniface DR, Cregg R, Zakrzewska JM. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). J Headache Pain 2015;16:563
72. Tatli M, Satici O, Kanpolat Y, Sindou M. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. Acta Neurochir (Wien) 2008;150(3):243–255
73. Bigder MG, Krishnan S, Cook EF, Kaufmann AM. Microsurgical rhizotomy for trigeminal neuralgia

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in MS patients: technique, patient satisfaction, and clinical outcomes. J Neurosurg 2018;130(6): 1877–1888
74. Ko AL, Ozpinar A, Lee A, Raslan AM, McCartney S, Burchiel KJ. Long-term efficacy and safety of internal neurolysis for trigeminal neuralgia without neurovascular compression. J Neurosurg 2015;122(5):1048–1057
75. Tronnier VM, Rasche D, Hamer J, Kienle AL, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery 2001;48(6):1261–1267, discussion 1267–1268
76. Puca A, Meglio M, Cioni B, Visocchi M, Vari R. Microvascular decompression for trigeminal neuralgia: prognostic factors [Internet]. In: Meyerson BA, Broggi G, Martin-Rodriguez J, Ostertag C, Sindou M, eds. Advances in Stereotactic and Functional Neurosurgery 10. Vienna: Springer Vienna; 1993:165–167. Accessed August 3, 2024 at: http://link.springer.com/10.1007/978-3-7091-9297-9_38
77. Youmans JR. Youmans & Winn Neurological Surgery. 8th ed. Philadelphia, PA: Elsevier; 2023
78. Barker TH, Stone JC, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI Evid Synth 2023;21(3):494–506
79. Olson S, Atkinson L, Weidmann M. Microvascular decompression for trigeminal neuralgia: recurrences and complications. J Clin Neurosci 2005;12(7):787–789
80. Huang Z, Pu B, Li F, et al. Analysis of failed microvascular decompression in patients with trigeminal neuralgia. J Neurol Surg B Skull Base 2020;81(5):567–571
81. Yamaki T, Hashi K, Niwa J, et al. Results of reoperation for failed microvascular decompression. Acta Neurochir (Wien) 1992;115(1-2):1–7
82. Lee SH, Levy EI, Scarrow AM, Kassam A, Jannetta PJ. Recurrent trigeminal neuralgia attributable to veins after microvascular decompression. Neurosurgery 2000;46(2):356–361, discussion 361–362
83. Rath SA, Klein HJ, Richter H-P. Findings and long-term results of subsequent operations after failed microvascular decompression for trigeminal neuralgia. Neurosurgery 1996;39(5):933–938, discussion 938–940
84. Rappaport ZH, Gomori JM. Recurrent trigeminal cistern glycerol injections for tic douloureux. Acta Neurochir (Wien) 1988;90(1-2):31–34
85. Park K-J, Kondziolka D, Berkowitz O, et al. Repeat gamma knife radiosurgery for trigeminal neuralgia. Neurosurgery 2012;70(2):295–305, discussion 305
86. Mendelson ZS, Velagala JR, Kohli G, Heir GM, Mammis A, Liu JK. Pain-free outcomes and durability of surgical intervention for trigeminal neuralgia: a comparison of Gamma Knife and microvascular decompression. World Neurosurg 2018;112:e732–e746
87. Henson CF, Goldman HW, Rosenwasser RH, et al. Glycerol rhizotomy versus gamma knife radiosurgery for the treatment of trigeminal neuralgia: an analysis of patients treated at one institution. Int J Radiat Oncol Biol Phys 2005; 63(1):82–90
88. Wang DD, Raygor KP, Cage TA, et al. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. J Neurosurg 2018;128(1):68–77
89. Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. J Neurosurg 2019;130(3):733–757
90. Burchiel KJ, Steege TD, Howe JF, Loeser JD. Comparison of percutaneous radiofrequency gangliolysis and microvascular decompression for the surgical management of tic douloureux. Neurosurgery 1981;9(2):111–119
91. Chen J-F, Lee S-T. Comparison of percutaneous trigeminal ganglion compression and microvascular decompression for the management of trigeminal neuralgia. Clin Neurol Neurosurg 2003; 105(3):203–208

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26 Treatment of TB Meningitis Should Be for at Least 18 Months

Debaleena Mukherjee, Alak Pandit, and Souvik Dubey

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* bacilli (Mtb), despite being a treatable infectious disease, remains a significant global health threat. As per the World Health Organization (WHO), it affected nearly 10.6 million people in 2022.[1] Although pulmonary TB (PTB) is the commonest presentation, it also infects other organs causing extrapulmonary tuberculosis (EPTB) including central nervous system tuberculosis (CNS-TB). Tuberculous meningitis (TBM) is the most common manifestation of CNS-TB, characterized by inflammation of the meninges encasing the brain and spinal cord.[2,3] TBM notoriously affects children less than 5 years of age and people living with HIV along with populations with immunodeficiency caused by aging, malnutrition, malignancy, alcoholism, and drugs (e.g., chronic steroid and TNF-alpha inhibitor use).[2,3]

CNS-TB accounts for 5 to 8% of EPTB cases in immunocompetent hosts with TBM accounting for 70 to 80% of CNS-TB cases. TBM accounts for approximately 1 to 2% of active cases of TB.[2,4–7] The other forms of CNS-TB include intracranial (tuberculomas [with or without TBM], tubercular abscess, tubercular encephalopathy) and extracranial (tubercular myelitis, spinal arachnoiditis, spinal tuberculoma, Pott's spine) manifestations.[4,6] TBM still remains a medical emergency causing mortality in approximately 25% and long-term morbidity in nearly 50%.[8,9]

Despite all major advancements in our understanding of the disease evolution, diagnosis, and management, at this junction we are still left with more questions unresolved than answers. The most pertinent issues are:

- Evolving understanding of the underlying pathogenesis—an interplay between an infective process and a dysregulated immune response.
- The putative effect of underlying immune responses on disease outcome and therapeutic choices including the appropriate anti-tubercular drug (ATD) regimens and host-directed immunomodulator therapies.
- Unresolved dilemma regarding the optimum duration of treatment in TBM.

Despite TBM being a pertinent problem, especially in low- and middle-income nations, very few well-designed studies have addressed these concerns to determine the appropriate drug regimens and duration of therapy. In this chapter, the authors have elaborated on the underlying pathogenesis and immunological phenomenon along with the current treatment trends to better delineate the therapeutic choices.

Pathogenesis

In the course of evolution over thousands of years, Mtb has possibly developed mechanisms to manipulate the human innate and adaptive immune responses, ensuring its survival and transmission. Although it can induce an effective disease-limiting response, it can also trigger a progressively destructive

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cascade. Mtb virulence and host genetic susceptibility, along with the delicate balance between protective and pathological immune responses at various stages of the innate and adaptive immunity pathways, determine the final outcome.[9–12]

TB is an airborne infection, with lungs being the primary site of involvement. Once Mtb enters the alveolar space, the innate immune system consisting of alveolar macrophages, neutrophils, and dendritic cells mount a response by releasing immune-signaling molecules and engulfing the mycobacteria. Cytokines and chemokines (TNF-alpha, IFN-gamma, MCP-1, IL-6, IL-1alpha/IL-1beta, IL-12p70, and IL-23) along with antimicrobial peptides (defensins, cathelicidin, and azurocidin) are released. Infected cells then migrate to lymphoid tissues, initiating the adaptive immune response where they activate antigen-specific T-cells that differentiate into cytokine-producing cells. They express different chemokine receptors and migrate away from the lymph nodes to reach sites of tissue inflammation. The T-cells migrate along chemokine gradients, colocate with Mtb-infected phagocytic cells, and release cytokines that activate the infected cells to kill the Mtb. The predominant role of $CD4^+$ T-cells lies in the maturation of macrophages and IFN-gamma production, which works along with TNF-alpha, IL-1, and IL-6 to aid the process and control infection. $CD8^+$ T-cells also contribute minorly to IFN-gamma production and act via cytolytic actions. Infected cells aggregate to form granulomas. Macrophages thus play a critical role in defense, with appropriate response resulting in containment of infection. However, phagocytosed Mtb can evade the efforts, resulting in its slow replication in the phagosome (latent infection phase) or dissemination. Immunity to TB depends on the rapid and optimum accumulation of phagocytes and T-cells at the site of infection, with crucial role played by TNF, IFN, and IL-1 family. A fine balance between the cytokines and their receptors plays a critical role in determining the containment of TB via granuloma formation versus dissemination and damage.[2,9–14]

Dissemination occurs via hematogenous route (bacillemia) following primary pulmonary infection, or reactivation of latent TB elsewhere in the body. During bacillemia, Mtb are scattered in the meninges and brain parenchyma resulting in formation of multiple granulomatous foci (tubercles).[15] Rich and McCordock in 1933 described granulomas in the brain and meninges and rarely in spinal cord and bone (Rich foci), which were the entry point of bacilli in the CNS. Rupture of subependymal and sub-pial foci leads to extension of infection into the cerebrospinal fluid (CSF) space, meninges, and vasculature.[16] Although TBM is commonly perceived as a complication of active progressive PTB, most adult cases result from reactivation of hidden foci of chronic TB of other organs which causes intermittent or chronic progressive bacillemia.[2,15]

How Mtb exactly invades the CNS remains elusive. The brain parenchyma is privileged in terms of immunity, containing only microglia, mast cells, and macrophages in health, while the CSF is comparatively less privileged. This is maintained by the barrier systems including blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier (BCSFB).[9] Damage to these results in infiltration of leukocytes and molecules. Mediators of BBB dysfunction include matrix metalloproteinases, vascular endothelial growth factor, caspases, and cytokines (TNF-α, IFN-γ, IL1-β, IL-6, IL-8). Mtb is postulated to gain access via receptor-mediated endocytosis, paracellular infiltration of free-floating bacilli, and Trojan horse phenomenon, where infected monocytes cross the barriers and infect neural tissue.[2,9,17–19] Mtb invades the CNS and causes direct damage to microglia, neurons, and astrocytes, setting off an aberrant host response. Microglia are unique tissue-resident macrophages which are postulated to play a crucial role in neuroinflammation. In adulthood they survey the parenchyma for damage-associated and

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pathogen-associated molecular patterns. Mtb-challenged microglia secrete various cytokines and chemokines. Although it plays an essential role in defense, it can also contribute to excess inflammation. It is hypothesized that aged microglia may have a phenotype which controls Mtb infection leading to lesser occurrence of TB in HIV-negative adults, while the incidence is greater in children.[2,9] The balance in the levels of the cytokines and immune responses especially in the CNS plays a crucial role in determining a favorable outcome versus a dysregulated immune response. Role of activation of microglia and inflammasome associated with the innate response is being increasingly studied, with increased levels being associated with TBM–immune reconstitution inflammatory syndrome (IRIS). Although TNF-α is known to play a protective role, in the CNS it also has potential to mediate damage. Elevated CSF neutrophils and their associated proteins (S100A8/A9) are also associated with poorer outcomes and TBM–IRIS.[9,20]

Importantly, several immune response genes are strongly genetically influenced. Polymorphisms in several host response genes such as TLR9, SIGIRR, TIRAP, TLR2, LTA4H, and MRC1 can influence the immune response and predispose to TBM.[11,20] Mendelian susceptibilities to mycobacterial diseases (MSMD) have been further recognized as an entity with selective susceptibility to poor virulent Mtb in the absence of overt immunodeficiency.[11,20,21]

The interplay between protective and pathological immune responses against Mtb raises significant concerns regarding the treatment. Are the clinico-radiological manifestations particularly the paradoxical worsening and frequent persistence of asymptomatic radiological lesions despite prolonged therapy a result of the infective process with or without drug resistance or due to a dysregulated immune response? Does this truly warrant prolongation of ATD or should we focus on targeted immunotherapies? Thus, well-designed studies are the need of the hour to determine the effect of the immunology on planning treatment regimens and durations.

Treatment Trends in Tuberculous Meningitis

TBM is a devastating illness with high fatality rates and neurological sequelae. Hence, its treatment is often started empirically on clinical suspicion with supportive CSF and radiological features. Modified Medical Research Council grade II/III TBM at presentation, HIV co-infection, delayed treatment initiation, drug resistance and noncompliance, and hydrocephalus and strokes are associated with poor outcomes.[7,22]

The optimum duration of therapy continues to be strongly debated.[3,7,19,20,23] As per majority of the guidelines the treatment regimens for TBM are derived from management of PTB, including an intensive and continuation phase, although longer duration of treatment is commonly advocated and practised.[24–38] The trend for longer treatment in TBM compared to PTB has largely been to prevent devastating neurological relapses and sequelae and achieve microbiological cure. Although in PTB 5% relapse rate is considered acceptable, in TBM any relapse must be avoided.[36,39] It is concerning that the reduced penetration of the BBB hinders CSF availability of some first-line and major second-line ATD. Slow clinico-radiological recovery, frequent persistence of CNS tuberculomas with or without meningitis, paradoxical worsening on ATD, and drug resistance and relapse have also led to the practice of different ATD regimens worldwide, with duration of treatment ranging between 6 and 24 months. Significant variation also exists with respect to doses as well as choice of the fourth drug in intensive phase.[36]

Although longer regimens are practiced to avoid devastating relapses and morbidity, they are associated with an increased possibility of drug-related adverse effects, noncompliance, increased cost for patients and health care systems, as well as nonavailability of

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medications, leading to search for shorter regimens. However, the latter have a perceived increased risk of relapse and death. Despite this crucial dilemma, well-designed randomized studies and evidences are still lacking, with most consensus guidelines recommending treatment for 9 to 12 months with further prolongation based on clinical judgment (**Table 26.1**).

Table 26.1 Summary of guidelines for management of drug-susceptible tuberculous meningitis

	Drug-susceptible tuberculosis meningitis			
	IP	**CP**	**Corticosteroids**	**Duration**
WHO (2010)[24] Treatment of Tuberculosis: Guidelines	New case: HRZ+ (E replaced by S) × 2 months	HR × 7–10 months	To be given unless drug resistance is suspected	9–12 months
WHO (2017 Update)[25] Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care	No modification		Adjuvant corticosteroid therapy with dexamethasone or prednisolone over 6–8 weeks should be used	9–12 months
WHO (2022)[26] Drug-Susceptible Tuberculosis Treatment	E favored over S		No modification	9–12 months
WHO (2010)[27] Rapid Advice: Treatment of Tuberculosis in Children	HRZE × 2 months	HR × 10 months	-	12 months
WHO (2014)[28] Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children	HRZE × 2 months	HR × 10 months	Recommended in all cases of TBM. Prednisone is used most frequently, in a dosage of 2 mg/kg daily, increased to 4 mg/kg daily in the case of the most seriously ill children (max. dosage of 60 mg/day) for 4 weeks. The dose should then be gradually reduced over 1–2 weeks before stopping.	12 months
WHO (2021)[29] WHO Issues Rapid Communication on Updated Guidance for the Management of TB in Children and Adolescents	HRZEto × 6 months			6 months
WHO (2022)[30] Management of Tuberculosis in Children and Adolescents	HRZE × 2 months (strong recommendation)	HR × 10 months	Dexamethasone or prednisolone tapered over 6 to 8 weeks should be used	12 months

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Table 26.1 *(Continued)*

	Drug-susceptible tuberculosis meningitis			
	IP	**CP**	**Corticosteroids**	**Duration**
	HRZEto × 6 months (conditional recommendation)			6 months
British Infection Society (2009)[31]	HRZE × 2 months	HR × at least 10 months	Should be given to all patients with TBM, regardless of disease severity. Insufficient evidence for routine use in all tuberculomas without meningitis, or with spinal cord tuberculosis. However, they may be helpful in patients whose symptoms are not controlled, or worsening, on ATD or who have acute spinal cord compression secondary to vertebral tuberculosis	12 months at least
NICE (2006)[32]	HRZ + fourth drug (e.g., E) × 2 months	HR × 10 months	Adults: Equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg Children: Equivalent to prednisolone 1–2 mg/kg, maximum 40 mg; to taper gradually, starting within 2–3 weeks of initiation	12 months
NICE (2011)[33]	No change in recommendation			12 months
ATS/CDC/IDSA (2003)[34]	Regimen 1: HRZE Regimen 2: HRZE Regimen 3: HRZE Regimen 4: HRE	Regimen 1a/1b: HR Regimen 1c: HRPT Regimen 2a: HR 2b: HRPT Regimen 3a:HR Regimen 4a/4b: HR	Steroid is recommended	9–12 months
ATS/CDC/IDSA (2016)[35]	HRZE × 2 months	HR × 7–10 months	Dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis	9–12 months

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Table 26.1 *(Continued)*

	Drug-susceptible tuberculosis meningitis			
	IP	**CP**	**Corticosteroids**	**Duration**
Index-TB Guidelines (2016)[36]	HRZE × 2 months	HRE × 7 months at least	HIV negative: Strong recommendation HIV positive: May be used in absence of opportunistic infections Duration: At least 4 weeks	2 + 7 months (low-quality evidence)*
Technical and operational guidelines for TB control in India (2016)[37]	New: HRZE × 2 months Previously treated: HRZES × 2 months + HRZE × 1 month	HRE × 4 months HRE × 5 months In case of CNS-TB extension of CP by 3–6 months	-	9–12 months 11–14 months
Training Module on Extrapulmonary Tuberculosis (2023)[38]	HRZS/HRZEx 2 months	HRE × at least 10 months	Dexamethasone 0.4 mg/kg/day IV. If not feasible oral dexamethasone 0.4 mg/kg/day or prednisolone 1mg/kg, tapering dose for total 8-12 weeks.	12 months 12–18 months in case of tuberculomas/brain abscess

Abbreviations: ATD, anti-tubercular drug; ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CP, continuation phase; E, ethambutol; Eto, ethionamide; H, isoniazid; IDSA, Infectious Disease Society of America; IP, intensive phase; NICE, National Institute for Clinical Excellence; R, rifampicin; S, streptomycin; TB, tuberculosis; TBM, tuberculous meningitis; WHO, World Health Organization; Z, pyrazinamide; RPT, rifapentine.
Note: *Technical Advisory Sub-committee for CNS-TB suggested an alternative approach to the CP: (a) recommend the use of pyrazinamide instead of ethambutol and (b) treatment in all patients for a total of at least 12 months.

Drug-Susceptible TBM in Adults

Currently, the intensive phase regimen for presumed drug-susceptible TBM consists of four drugs for 2 months including isoniazid (H), rifampicin (R), pyrazinamide (Z), and either streptomycin (S) or ethambutol (E), followed by 7 to 10 months of isoniazid and rifampicin at standard doses. Isoniazid and pyrazinamide are drugs with high CNS penetration (90–95% and 95–100%) and bactericidal activity with a key role in reducing treatment duration. Although rifampicin has poor CNS penetration (5–25%) and multiple drug interactions, its crucial role is reflected by the high mortality of rifampicin-resistant TBM.[3,20,23] With respect to the choice of the fourth drug, streptomycin and ethambutol have poor CNS penetration in the absence of inflammation (10–20% and 10–50% respectively), with importance mainly in the background of isoniazid resistance. Although WHO 2010 guidelines suggested streptomycin instead of ethambutol as the fourth drug, the side effects including vestibulopathy significantly reduced its uses.[24] Other potential choices include fluoroquinolones like levofloxacin and moxifloxacin with good CSF

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penetration and safety profiles. Although major benefit lies with its use in isoniazid-resistant TB, there is inadequate data to suggest that it improves survival in drug-sensitive TB. Some centers use ethionamide (Eto), which penetrates both healthy and inflamed meninges, with lesser sides effects and is effective in isoniazid resistance.[3,20,23]

There still exists considerable variability in treatment durations. Satoskar and Bhandarkar[40] had earlier suggested treatment for 24 to 36 months. American Trudeau Society (1954), Singhal, and Parsons proposed regimens for 18 to 24 months.[41–43] Goel et al emphasized that duration be at least 24 months, having observed that 35/37 patients requiring readmission for relapses had received therapy less than 24 months.[44] Girgis et al, while comparing the efficacy of steroid in TBM, also provided a course of HE for 24 months.[45] On the other hand, several authors adopted regimens for 12 to 18 months,[46–52] 9 months,[53–64] and 6 months,[65–69] showing varying proportions of mortality and neurological sequelae. Significant heterogeneity exists between the studies especially with relation to study designs, disease severity, co-infection with HIV, treatment regimens, and durations.[7] Although some studies show comparable results between short and longer courses, some suggest the contrary (**Table 26.2**). Doğanay et al compared short-course (8 months) versus

Table 26.2 Regimens and durations of treatment given in previous important studies

Study	Regimen and duration	Conclusion
Goel et al[44] India, *n* = 1086	3HRZS + 6HRE + 15HE (**24 months**)	35 patients readmitted with relapse received treatment less than 2 years; nearly 67% total patients lost to follow-up with duration of therapy received and relapse status unknown
Girgis et al[45] Egypt, *n* = 280	24HE; 6 weeks S (**24 months**) Compared ATD + steroid versus ATD alone	Significantly lower mortality and sequelae with steroids; overall mortality was 54% and sequelae was 14.6%
Ramachandran et al[79] India, *n* = 180	Regimen 1: 2HRS + $4S_2$HE + 6HE Regimen 2: 2HRZS + 10HE Regimen 3: $2HR_2$SZ + 10HE (**12 months**)	Mortality, 27%; sequelae, 39%; relapse, none (119 patients were followed up over 4.5–8 years, showing no relapse.[80])
Doğanay et al[70] Turkey, *n* = 72	Short course: 2HRZS + 6HR (**8 months**) Long course: 4 ATD for 4–6 months followed by 2–3 ATD (**12–16 months**)	Mortality: 13.5% in short-course therapy and 5.7% in the long course Sequelae: 30.7% in short course, 31.2% in long course Relapse: None
Cagatay et al[47] Turkey, *n* = 42	H × 12 R × 12 Z × 2–3 E × 3–6 (**12 months**)	Mortality, 7.14%; sequelae, 36%
Pehlivanoglu et al[48] Turkey, *n* = 160	12–18HRZE (**12–18 months**)	Mortality, 17%; sequelae, 13%
Chen et al[49] China, *n* = 38	2HRZE + 10–16HRE (**12–18 months**)	TBM with cerebral infarction versus those without had mortality (30.8% vs. 16%) and overall poor brain sequelae (69.2% vs. 8%)
Misra et al[50] India, *n* = 74	6HRZE + 12HR (**18 months**)	29% of MV patients survived and had poor outcome at 3 months; but in the non-MV group, all the patients survived, and only 11% had poor outcome

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Table 26.2 *(Continued)*

Study	Regimen and duration	Conclusion
Tai et al[51] Malaysia, *n* = 41	2HRZE + 10–16HR (**12–18 months**)	61% with paradoxical reactions improved, 26% mortality, 13% sequelae
Li et al[52] China, *n* = 154	2–4HRZE + 6–12HR (**8–16 months**)	Mortality, 21%; poor outcome, 31%
Phuapradit and Vejjajiva[53] Thailand, *n* = 28	2HRZS + 7HR (**9 months**)	Mortality: 8.3% Sequelae: 12.5% Relapse: None over 12–29 months
Hosoğlu et al[54] Turkey, *n* = 101	Group 1: 2–3HRSZ + ≥6HR Group 2: 2–3HRSE + ≥6 HR (**at least 8–9 months**)	Mortality, 43.5%; sequelae, 20.8%
Thwaites et al[55] Vietnam, *n* = 545	Group 1: 3HRZS + 6HRZ Group 2: 3HRZE + 6HRZ (**9 months**)	Treatment with dexamethasone was associated with decreased mortality but not morbidity Overall mortality was 36.5%, 10.3% severe disability, 16.3% relapse
Torok et al[56] Vietnam, *n* = 58 (HIV+ TBM)	Group 1: 3HRZE + 6HRZ Group 2: 3HRZES + 6HRZ (**9 months**)	Mortality was 67.2%
Török et al[57] Vietnam, *n* = 253 (HIV+ TBM) **RCT**	Group 1: 3HRZE + 6HR Group 2: 3HRZES + 6HR (**9 months**)	Immediate ART initiation does not improve outcome in HIV-TBM
Iype et al[61] India, *n* = 43	Category 1: $2HRZE_3 + 7HR_3$ or $2HRZS_3 + 7HR_3$ (**9 months**) Category 2: $2(HREZS)_3 + 1(HREZ)_3 + 7(HR)_3$ (**10 months**)	18.6% mortality, comparable to daily regimens 1 patient relapsed with TBM 3 months after treatment completion 18.6% paradoxical reactions
Heemskerk et al[63] Vietnam, *n* = 817, **RCT**	Group 1: 3HRZE + 6HR (R at 10 mg/kg) Group 2: 3HRZE + 6HR (R at 15 mg/kg/day,+ L at 20 mg/kg/day for first 8 weeks) (**9 months**)	Intensified regimen was not associated with higher survival compared to standard regimen
Raberahona et al[64] Madagascar, *n* = 75	Group 1: **2**HRZE + Continuation phase was 6HE before 2012 and 4HR after 2012 Group 2: 2HRZES + HRZE	Mortality rate was 28%
Jacobs et al[81] Bangkok, *n* = 53	Regimen A: 2HSE + 10HE or 2RSE + 10 RE (**12 months**) Regimen B: 2HRS + 7HR (**9 months**) Regimen C: 2HRZS + 4HR (**6 months**)	Mortality, 20.8% (11/53); sequelae, 35.7% (15/42) Negative outcome and sequelae significantly lower in Regimen C containing pyrazinamide compared to those without
Alarcón et al[65] Ecuador, *n* = 28	2HRZ + 4HR (**6 months**)	Mortality, 32.1%; sequelae, 10.7%
Chotmongkol[66] Thailand, *n* = 29	4HRZS + 2HR (**6 months**)	Mortality, 16% (4/25); sequelae,14.2% (3/21)
Donald et al[82] South Africa, *n* = 95	6HR + Z (40 mg/kg) + Eto (20 mg/kg) (**6 months**)	Young children can be treated safely without overt toxicity and with a low risk of relapses

Abbreviations: ART, antiretroviral therapy; ATD, anti-tubercular drug; E, ethambutol; Eto, ethionamide; H, isoniazid; MV, mechanical ventilation; R, rifampicin; RCT, randomized controlled trial; S, streptomycin; TBM, tuberculous meningitis; Z, pyrazinamide.

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long-course (12–16 months) therapy showing mortality rates (13.5% vs. 5.7%) and comparable neurological sequelae.[70] van Loenhout-Rooyackers et al reviewed studies between 1978 and 1999 comparing 6 months versus greater than 6 months regimens for TBM, suggesting 6-month treatment is sufficient for TBM with fully susceptible mycobacteria with no difference in 2-year relapse rates.[71] Jullien et al reviewed and compared short-course regimens versus prolonged course in TBM including 18 studies and analyzed 20 cohorts. Relapses were uncommon in both the groups. Clinical cure and adherence were higher in the cohorts treated for 6 months. Although mortality was higher in the longer treatment group, most deaths occurred in the initial 6 months, and was unlikely to be related to treatment duration.[72]

Goyal et al (2019) studied treatment patterns at a tertiary care institute in India and found ATD durations ranging from 9 to 36 months.In this study, proportion of patients with good outcome was comparable whether the intensive phase was for 2 or 3 months or all drugs were continued for more than 12 months or whether the duration of treatment was 12 months or more. There was no difference in mortality in patients who received treatment for 12 months or more.[73]

A randomized controlled trial (RCT), the INSHORT trial, is currently ongoing to study the efficacy of intensified short-course regimen with high dose rifampicin (HDR) and moxifloxacin (2HDR-moxifloxacin-HZ + 4HRZ) along with steroids with and without aspirin versus 12 months of standard ATD regimen (2HRZE + 7–10HRE) with steroids.[74] The INTENSE-TBM study is a phase III RCT studying the efficacy of intensified regimen with high-dose rifampicin and linezolid HDRLHZE (up to week 8) + HR(week 9-40) versus standard treatment of HRZE (up to week 8) + HR (week 9-40) in reducing mortality.[75]

Drug-Susceptible TBM in Children

Children with TBM usually require higher doses per kg body weight of drugs. Significant controversy continues to surround the appropriate doses, especially rifampicin—whether >10 mg/kg body weight should be used in both children and adults. The fourth choice of drug also varies. In children, ethambutol is often replaced by either an aminoglycoside or ethionamide because of difficulty in monitoring ethambutol-associated optic neuritis. Fluoroquinolones have possible potential, but studies are needed to prove their efficacy and safety in children.[76,77]

WHO Rapid Advice: Treatment of Tuberculosis in Children (2010) and WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children (2014) recommended that children with TBM should receive standard HRZE for 2 months followed by 10 months of HR at standard doses as per PTB.[27,28] Lorin et al suggested that isoniazid and rifampicin should be used in every regimen for 2 years and at least 1 year respectively.[78] Ramachandran et al studied three different regimens for 12 months in children with TBM with no relapses over 4.5 to 8 years.[79,80] Jacobs et al compared three regimens in children of durations 12, 9, and 6 months, with the last regimen containing pyrazinamide showing lower negative outcomes and sequelae compared to the other regimens without it.[81] Donald et al used an intensified short-course regimen of H, R, Z (40 mg/kg), and Eto (20 mg/kg) for 6 months, showing decreased relapse risk and adverse effects of drugs.[82] van Toorn et al used intensified short-course treatment (6RHZEto for HIV-negative and 9RHZEto for HIV-infected) and found it to be sufficient and safe in children with drug-susceptible TBM. High oral dose rifampicin (20 mg/kg/d) for 6 to 9 months was well tolerated by children.[83]

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Several studies have demonstrated that higher doses of rifampicin (intravenous/oral) have increased plasma and CSF rifampicin levels without added adverse outcomes[84–86] and reduced mortality in children with TBM.[87,88] However, study by Heemskerk et al, with higher rifampicin dose (15 mg/kg) and levofloxacin (20 mg/kg) for the initial 2 months in comparison to standard regimen, did not find significant difference in mortality.[63] The 2021 WHO rapid communication recommended a shorter intensive regimen composed of 6HRZEto in children and adolescents with microbiologically confirmed or clinically diagnosed, presumed drug-susceptible TBM as an alternative to the previously recommended 12-month regimen.[29] In 2022, the WHO strongly recommended 2HRZE + 10HR for children and adolescents with TBM with a conditional recommendation for 6HRZEto.[30] Sulis et al, in their systematic review and meta-analysis involving more than 1000 participants, showed lower mortality (5% vs. 23.9%), higher treatment success rate (94.6% vs. 75.4%) but greater neurological sequelae among survivors (66% vs. 36.3%) with shortened 6-month regimen compared to traditional 12 months one.[89] SURE is an ongoing RCT to study the safety and efficacy of short-course regimen (6HRZ + levofloxacin) versus standard regimen (2HRZE + 10HR) in children with TBM. It is also studying the role of aspirin in reducing disability in children.[90]

Drug-Resistant TBM

Multidrug resistant (MDR) TBM is defined as resistance to at least isoniazid and rifampicin. There is severe dearth of studies and controlled trials for the treatment of MDR-TBM, and limited data on the CSF penetrance of second-line and newer anti-TB drugs.[3] Thus, the treatment guidelines for MDR-TBM are largely extrapolated from treatment protocols of pulmonary MDR-TB. The treatment is best guided by drug-susceptibility testing and the knowledge of penetration of the BBB by the drugs.[3,91]

For treatment of isoniazid-resistant TBM, intensive phase treatment with daily rifampicin, ethambutol, pyrazinamide, and a fluoroquinolone for 2 months followed by a continuation phase of rifampicin, pyrazinamide, and a fluoroquinolone for at least 10 months is suggested.[76]

WHO (2010) suggested that for MDR/rifampicin-resistant (RR) TBM, regimen should include any first-line drugs to which the organism is susceptible with the addition of an injectable agent (aminoglycoside or capreomycin), a fluoroquinolone, and then adding a second-line agent to make a regimen of at least four effective drugs. Moreover, the duration of therapy should be extended to 18 to 24 months, depending on the clinical response to treatment, the severity of the illness, and the patient's immune status.[24] WHO 2022 update recommends treatment is best guided by drug-susceptibility testing. It continues to suggest longer regimen for 18 to 20 months, with intensive phase of four likely effective drugs (three of group A and at least one of group B) and a continuation phase of at least three drugs. If four effective drugs are not achieved using groups A and B, group C can be used. Although bedaquiline can be added in all age groups, effectiveness of co-administration of bedaquiline and delamanid is less known.[92,93]

CNS Tuberculoma

The Index-TB guidelines suggested that ATD be given for 9 to 12 months initially, with monitoring of response via neuroimaging at 3 months and 9 to 12 months. The training module for extrapulmonary TB advised 12 to 18 months of treatment. Further management should be adjusted as per clinico-radiological response. Paradoxical reaction with increase in lesions size and number usually occurs in the first 3 months of starting the therapy, requiring treatment with steroids and ATD continuation.

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Treatment failure should be suspected when lesions either increase or fail to reduce in size after 3 to 6 months of optimum therapy. The treating clinician must weigh the risks and benefits of biopsy against starting therapy empirically for MDR-TB, or managing along lines of suspected paradoxical reactions.[36,38]

CNS-TB, Paradoxical Manifestations and IRIS

The paradoxical response to ATD is characterized by the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a CNS-TB patient who initially improved with ATD. IRIS refers to a paradoxical deterioration following the initiation of antiretroviral therapy in patients co-infected with HIV. These must be differentiated from treatment failure, multidrug resistance, drug toxicity, or clinical deterioration due to other etiology.[51,94,95]

It is believed to result from direct effect of the mycobacterial antigens and exaggerated human host response. Therapy-induced increased Mtb-specific TH1 cells in CSF and blood after 2 and 4 weeks respectively, excessive stimulation of the humoral and cell-mediated immunity by antigens from dead bacteria, increased TNF-alpha levels, high CSF neutrophil counts, and regulatory T-cell dysfunction are likely contributory.[51]

It usually develops after approximately 2 weeks of treatment, ranging between 1 and 9 months.[38,51] Although IRIS is notorious in HIV-infected patients, paradoxical reactions are being increasingly reported in HIV-negative TBM patients. The identification of paradoxical reaction is essential, so as not to mistake it as treatment failure or drug resistance as it does not necessarily adversely affect the outcome always. Although corticosteroids and ATD continuation is mostly beneficial, some forms may be devastating requiring further immunomodulator therapies.

Conclusion

In comparison to PTB, adequate evidence is lacking to guide optimal treatment of TBM. Due to lack of consensus guidelines, contemporary researchers have long used arbitrary durations of treatment with varying outcomes. The entire focus of recent TBM trials have been to optimize CNS drug penetration using alternative regimens using higher doses and/or shorter durations, while minimizing adverse effects. A large amount of uncertainty thus continues to ensue regarding the appropriate duration. As we continue to unravel how Mtb manipulates the immune system, it is an important concern whether our focus should be on the infective process alone or also on targeting the aberrant immune responses. Thus, well-designed studies are the need of the hour to determine the optimum drugs and duration of therapy for TBM.

References

1. WHO Global Tuberculosis Report. 2023. Accessed at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis
2. Hokeness S, Lanni F, Glycenfer J, et al. Tuberculous meningitis: an update on the pathogenesis and neuroimmunology. Curr Trop Med Rep 2024; 11(1):1–10
3. Marx GE, Chan ED. Tuberculous meningitis: diagnosis and treatment overview. Tuberc Res Treat 2011;2011:798764
4. Gupta M, Tobin EH, Munakomi S. CNS Tuberculosis. In StatPearls. StatPearls Publishing; 2024. Accessed at: http://www.ncbi.nlm.nih.gov/books/NBK585138/
5. Mezochow A, Thakur K, Vinnard C. Tuberculous meningitis in children and adults: new insights for an ancient foe. Curr Neurol Neurosci Rep 2017; 17(11):85
6. Ingole R, Garg RK, Malhotra HS, et al. Spectrum of central nervous system tuberculosis: an experience from a large tertiary care institution of India. Indian J Tuberc 2019;66(1):49–57
7. Wang M-G, Luo L, Zhang Y, Liu X, Liu L, He JQ. Treatment outcomes of tuberculous meningitis

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in adults: a systematic review and meta-analysis. BMC Pulm Med 2019;19(1):200
8. Seid G, Alemu A, Dagne B, Gamtesa DF. Microbiological diagnosis and mortality of tuberculosis meningitis: systematic review and meta-analysis. PLoS One 2023;18(2):e0279203
9. Barnacle JR, Davis AG, Wilkinson RJ. Recent advances in understanding the human host immune response in tuberculous meningitis. Front Immunol 2024;14:1326651
10. Manyelo CM, Solomons RS, Walzl G, Chegou NN. Tuberculous meningitis: pathogenesis, immune responses, diagnostic challenges, and the potential of biomarker-based approaches. J Clin Microbiol 2021;59(3):e01771–e20
11. de Martino M, Lodi L, Galli L, Chiappini E. Immune response to Mycobacterium tuberculosis: a narrative review. Front Pediatr 2019;7:350
12. Domingo-Gonzalez R, Prince O, Cooper A, Khader SA. Cytokines and chemokines in Mycobacterium tuberculosis infection. Microbiol Spectr 2016;4(5): 10.1128/microbiolspec.tbtb2-0018–2016
13. Orme IM, Robinson RT, Cooper AM. The balance between protective and pathogenic immune responses in the TB-infected lung. Nat Immunol 2015;16(1):57–63
14. Arranz-Trullén J, Lu L, Pulido D, Bhakta S, Boix E. Host antimicrobial peptides: the promise of new treatment strategies against tuberculosis. Front Immunol 2017;8:1499
15. Leonard JM. Central nervous system tuberculosis. Microbiol Spectr 2017;5(2)
16. Rich AR, McCordock HA. The pathogenesis of tuberculous meningitis. Bull Johns Hopkins Hosp 1933;52:5–37
17. van Leeuwen LM, Boot M, Kuijl C, et al. Mycobacteria employ two different mechanisms to cross the blood-brain barrier. Cell Microbiol 2018;20(9):e12858
18. Yang J, Ran M, Li H, et al. New insight into neurological degeneration: inflammatory cytokines and blood-brain barrier. Front Mol Neurosci 2022;15:1013933
19. Huynh J, Donovan J, Phu NH, Nghia HDT, Thuong NTT, Thwaites GE. Tuberculous meningitis: progress and remaining questions. Lancet Neurol 2022;21(5):450–464
20. Wilkinson RJ, Rohlwink U, Misra UK, et al; Tuberculous Meningitis International Research Consortium. Tuberculous meningitis. Nat Rev Neurol 2017;13(10):581–598
21. Rosain J, Kong X-F, Martinez-Barricarte R, et al. Mendelian susceptibility to mycobacterial disease: 2014-2018 update. Immunol Cell Biol 2019;97(4):360–367
22. Moodley S, Dlwati MS, Bhigjee AI. Treatment of tuberculous meningitis in adults: is the duration of intensive-phase therapy adequate? S Afr Med J 2021;111(5):412–415
23. Seddon JA, Tugume L, Solomons R, Prasad K, Bahr NC; Tuberculous Meningitis International Research Consortium. The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res 2019;4:167
24. World Health Organization. Treatment of Tuberculosis: Guidelines. World Health Organization; 2010. Accessed at: https://iris.who.int/handle/10665/44165
25. World Health Organization. Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care, 2017 Update. World Health Organization; 2017. Accessed at: https://iris.who.int/handle/10665/255052
26. WHO consolidated guidelines on tuberculosis: Module 4: treatment: drug-susceptible tuberculosis treatment. 2022. Accessed July 28, 2024 at: https://www.who.int/publications/i/item/9789240048126
27. Rapid advice: Treatment of tuberculosis in children. 2010. Accessed July 28, 2024 at: https://iris.who.int/handle/10665/44444
28. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd ed. World Health Organization; 2014. Accessed at: https://iris.who.int/handle/10665/112360
29. WHO issues rapid communication on updated guidance for the management of TB in children and adolescents. 2021. Accessed July 28, 2024 at: https://www.who.int/news/item/26-08-2021-who-issues-rapid-communication-on-updated-guidance-for-the-management-of-tb-in-children-and-adolescents
30. WHO consolidated guidelines on tuberculosis: Module 5: management of tuberculosis in children and adolescents. 2022. Accessed July 28, 2024 at: https://www.who.int/publications/i/item/9789240046764
31. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis

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and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009;59(3):167–187
32. Management of non-respiratory tuberculosis. In: Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control. NICE Clinical Guidelines, No. 117. National Collaborating Centre for Chronic Conditions (UK); Centre for Clinical Practice at NICE (UK). National Institute for Health and Clinical Excellence (UK); 2006. Accessed at: https://www.ncbi.nlm.nih.gov/books/NBK97856/
33. National Collaborating Centre for Chronic Conditions (UK) & Centre for Clinical Practice at NICE (UK). Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control. National Institute for Health and Clinical Excellence (UK); 2011. Accessed at: http://www.ncbi.nlm.nih.gov/books/NBK97852/
34. Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. 2003. Accessed July 29, 2024 at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm
35. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016;63(7):e147–e195
36. Index-TB Guidelines: Guidelines on Extrapulmonary Tuberculosis in India. 2016. Accessed July 28, 2024 at: https://iris.who.int/handle/10665/278953
37. TOG-Chapter 4-Treatment of TB—Central Tuberculosis Division. 2016. Accessed July 29, 2024 at: https://tbcindia-wp.azurewebsites.net/tog-chapter-4-treatment-of-tb/
38. Training Module on Extrapulmonary Tuberculosis. 2023. Accessed July 29, 2024 at: https://tbcindia.mohfw.gov.in/wp-content/uploads/2023/05/7702334778Training_Module_on_Extrapulmonary_TB_-_Book_24032023.pdf
39. Donald PR. The chemotherapy of tuberculous meningitis in children and adults. Tuberculosis (Edinb) 2010;90(6):375–392
40. Satoskar RS, Bhandarkar SD. Pharmacology and Pharmacotherapeutics. Bombay: Popular Prakashan; 1986
41. American Trudeau Society : Statement by committee on therapy concerning treatment of tuberculous meningitis. Am Rev Tuberc 1954;70:756–758 https://hdl.handle.net/2027/uc1.b2939416
42. Singhal BS. Controversies in the diagnosis and management of tuberculous meningitis in adults. In: Merchant SM, ed. Controversies in Tuberculosis. Bombay: Sir Hurkisondas Nurrotamdas Hospital Medical Research Society; 1980:77–83
43. Parsons M. The treatment of tuberculous meningitis. Tubercle 1989;70(2):79–82
44. Goel A, Pandya SK, Satoskar AR. Whither short-course chemotherapy for tuberculous meningitis? Neurosurgery 1990;27(3):418–421
45. Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatr Infect Dis J 1991;10(3):179–183
46. Chan KH, Cheung RTF, Fong CY, Tsang KL, Mak W, Ho SL. Clinical relevance of hydrocephalus as a presenting feature of tuberculous meningitis. QJM 2003;96(9):643–648
47. Cagatay AA, Ozsut H, Gulec L, et al. Tuberculous meningitis in adults -experience from Turkey: Tuberculous Meningitis in Adults. Int J Clin Pract 2004;58(5):469–473
48. Pehlivanoglu F, Yasar KK, Sengoz G. Tuberculous meningitis in adults: a review of 160 cases. ScientificWorldJournal 2012;2012:169028
49. Chen C-H, Chang Y-J, Sy H-N, Chen WL, Yen HC. Risk assessment of the outcome for cerebral infarction in tuberculous meningitis. Rev Neurol (Paris) 2014;170(8-9):512–519
50. Misra UK, Kalita J, Betai S, Bhoi SK. Outcome of tuberculous meningitis patients requiring mechanical ventilation. J Crit Care 2015;30(6):1365–1369
51. Tai MS, Nor HM, Kadir KAA, et al. Paradoxical manifestation is common in HIV-negative tuberculous meningitis. Medicine (Baltimore) 2016;95(1):e1997
52. Li K, Tang H, Yang Y, et al. Clinical features, long-term clinical outcomes, and prognostic factors of tuberculous meningitis in West China: a multivariate analysis of 154 adults. Expert Rev Anti Infect Ther 2017;15(6):629–635
53. Phuapradit P, Vejjajiva A. Treatment of tuberculous meningitis: role of short-course chemotherapy. Q J Med 1987;62(239):249–258

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54. Hosoğlu S, Ayaz C, Geyik MF, Kökoğlu OF, Ceviz A. Tuberculous meningitis in adults: an eleven-year review. Int J Tuberc Lung Dis 1998;2(7):553–557
55. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351(17):1741–1751
56. Torok ME, Chau TTH, Mai PP, et al. Clinical and microbiological features of HIV-associated tuberculous meningitis in Vietnamese adults. PLoS One 2008;3(3):e1772
57. Török ME, Yen NTB, Chau TTH, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)–associated tuberculous meningitis. Clin Infect Dis 2011;52(11): 1374–1383
58. Sinha MK, Garg RK, Anuradha HK, et al. Vision impairment in tuberculous meningitis: predictors and prognosis. J Neurol Sci 2010;290(1-2):27–32
59. Sharma P, Garg RK, Verma R, Singh MK, Shukla R. Incidence, predictors and prognostic value of cranial nerve involvement in patients with tuberculous meningitis: a retrospective evaluation. Eur J Intern Med 2011;22(3):289–295
60. Raut T, Garg RK, Jain A, et al. Hydrocephalus in tuberculous meningitis: incidence, its predictive factors and impact on the prognosis. J Infect 2013;66(4):330–337
61. Iype T, Pillai AK, Cherian A, et al. Major outcomes of patients with tuberculous meningitis on directly observed thrice a week regime. Ann Indian Acad Neurol 2014;17(3):281–286
62. Jha SK, Garg RK, Jain A, Malhotra HS, Verma R, Sharma PK. Definite (microbiologically confirmed) tuberculous meningitis: predictors and prognostic impact. Infection 2015;43(6):639–645
63. Heemskerk AD, Bang ND, Mai NTH, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. N Engl J Med 2016;374(2):124–134
64. Raberahona M, Rakotoarivelo RA, Razafinambinintsoa T, Andrianasolo RL, Randria MJ. Clinical features and outcome in adult cases of tuberculous meningitis in tertiary care hospital in Antananarivo, Madagascar. BioMed Res Int 2017;2017:9316589
65. Alarcón F, Escalante L, Pérez Y, Banda H, Chacón G, Dueñas G. Tuberculous meningitis. Short course of chemotherapy. Arch Neurol 1990;47(12): 1313–1317
66. Chotmongkol V. Treatment of tuberculous meningitis with 6-month course of chemotherapy. Southeast Asian J Trop Med Public Health 1991;22(3):372–374
67. Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. J Med Assoc Thai 1996;79(2):83–90
68. Katrak SM, Shembalkar PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. J Neurol Sci 2000;181(1-2):118–126
69. Hsu PC, Yang CC, Ye JJ, Huang PY, Chiang PC, Lee MH. Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. J Microbiol Immunol Infect 2010;43(2):111–118
70. Doğanay M, Calangu S, Turgut H, Bakir M, Aygen B. Treatment of tuberculous meningitis in Turkey. Scand J Infect Dis 1995;27(2):135–138
71. van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis 2001;5(11):1028–1035
72. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. Cochrane Library. 2016. Accessed July 29, 2024 at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012091.pub2/full
73. Goyal V, Elavarasi A, Abhishek, Shukla G, Behari M. Practice trends in treating central nervous system tuberculosis and outcomes at a tertiary care hospital: a cohort study of 244 cases. Ann Indian Acad Neurol 2019;22(1):37-46
74. Inbaraj LR, Manesh A, Ponnuraja C, Bhaskar A, Srinivasalu VA, Daniel BD. Comparative evaluation of intensified short course regimen and standard regimen for adults TB meningitis: a protocol for an open label, multi-center, parallel arms, randomized controlled superiority trial (INSHORT trial). Trials 2024;25(1):294
75. Maitre T, Bonnet M, Calmy A, et al. Intensified tuberculosis treatment to reduce the mortality of HIV-infected and uninfected patients with tuberculosis meningitis (INTENSE-TBM): study protocol for a phase III randomized controlled trial. Trials 2022;23(1):928
76. Slane VH, Unakal CG. Tuberculous Meningitis. 2022 Nov 18. In: StatPearls [Internet]. Treasure Island

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(FL): StatPearls Publishing; 2024 Jan. Accessed at: http://www.ncbi.nlm.nih.gov/books/NBK541015/
77. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: clinical management & outcome. Indian J Med Res 2019;150(2):117–130
78. Lorin MI, Hsu KHK, Jacob SC. Treatment of tuberculosis in children. Pediatr Clin North Am 1983;30(2):333–348
79. Ramachandran P, Duraipandian M, Nagarajan M, Prabhakar R, Ramakrishnan CV, Tripathy SP. Three chemotherapy studies of tuberculous meningitis in children. Tubercle 1986;67(1):17–29
80. Ramachandran P, Duraipandian M, Reetha AM, Mahalakshmi SM, Prabhakar R. Long-term status of children treated for tuberculous meningitis in south India. Tubercle 1989;70(4):235–239
81. Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K. Intensive short course chemotherapy for tuberculous meningitis. Pediatr Infect Dis J 1992;11(3):194–198
82. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 1998;2(9):704–711
83. van Toorn R, Schaaf HS, Laubscher JA, van Elsland SL, Donald PR, Schoeman JF. Short intensified treatment in children with drug-susceptible tuberculous meningitis. Pediatr Infect Dis J 2014;33(3):248–252
84. Savic RM, Ruslami R, Hibma JE, et al. Pediatric tuberculous meningitis: model-based approach to determining optimal doses of the anti-tuberculosis drugs rifampin and levofloxacin for children. Clin Pharmacol Ther 2015;98(6):622–629
85. Dian S, Yunivita V, Ganiem AR, et al. Double-blind, randomized, placebo-controlled phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. Antimicrob Agents Chemother 2018;62(12):e01014–e01018
86. Cresswell FV, Meya DB, Kagimu E, et al. High-dose oral and intravenous rifampicin for the treatment of tuberculous meningitis in predominantly human immunodeficiency virus (HIV)-positive Ugandan adults: a phase II open-label randomized controlled trial. Clin Infect Dis 2021;73(5):876–884
87. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis 2013;13(1):27–35
88. Svensson EM, Dian S, Te Brake L, et al. Model-based meta-analysis of rifampicin exposure and mortality in Indonesian tuberculous meningitis trials. Clin Infect Dis 2020;71(8):1817–1823
89. Sulis G, Tavaziva G, Gore G, et al. Comparative effectiveness of regimens for drug-susceptible tuberculous meningitis in children and adolescents: a systematic review and aggregate-level data meta-analysis. Open Forum Infect Dis 2022;9(6):ofac108
90. ISRCTN. SURE: Short intensive treatment for children with tuberculous meningitis. ISRCTN40829906. 2022. https://doi.org/10.1186/ISRCTN40829906
91. Davis A, Meintjes G, Wilkinson RJ. Treatment of tuberculous meningitis and its complications in adults. Curr Treat Options Neurol 2018;20(3):5
92. Vanino E, Granozzi B, Akkerman OW, et al. Update of drug-resistant tuberculosis treatment guidelines: a turning point. Int J Infect Dis 2023;130(Suppl 1): S12–S15
93. Organization WH. WHO consolidated guidelines on tuberculosis. Module 4: Treatment—drug-resistant tuberculosis treatment, 2022 update. World Health Organization; 2022. https://www.who.int/publications/i/item/9789240063129
94. Garg RK, Malhotra HS, Kumar N. Paradoxical reaction in HIV negative tuberculous meningitis. J Neurol Sci 2014;340(1-2):26–36
95. Singh AK, Malhotra HS, Garg RK, et al. Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. BMC Infect Dis 2016;16:306

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27 Ocular Myasthenia Gravis Should Be Treated as Aggressively as Generalized Myasthenia Gravis

Jasodhara Chaudhuri and Kartik C. Ghosh

Introduction

Myasthenia gravis is an immune-mediated disease characterized by antibodies against acetylcholine receptors and other related functional proteins at post-synaptic neuromuscular junction (NMJ). The overall incidence of ocular myasthenia gravis (OMG) based on a population-based study is 1.13 per 100,000 per year.[1] Almost 50% of myasthenia patients present initially with ocular symptoms and eventually progress to generalized myasthenia gravis (GMG) in 30 to 60% cases.[2] OMG is characterized by fluctuating ptosis and diplopia. The diagnosis is established by clinical signs and symptoms and positive test for specific antibodies. There is lack of evidence-based guidelines on comprehensive management of OMG. In this chapter we intend to discuss the recent updates on diagnosis and management of OMG.

History and Epidemiology of Myasthenia Gravis

Dr. Jolly, a German physician, was the first to coin the term myasthenia gravis in 1895. Treatment of myasthenia became possible in 1934. Dr. Simpson and Dr. Nastuck discussed the role of immune system in the pathogenesis of myasthenia gravis.[3] Myasthenia may affect population of any age and ethnicity, but it is unusual to affect the age group below 10 years and above 70 years. As compared to GMG, in OMG there is male preponderance, especially after the age of 40 years.[4] In India, myasthenia gravis is seen more in males than in females; the age of onset in females is in the third decade, and that in males is seen to be from the sixth decade onwards.[5]

Pathophysiology and Clinical Aspects

NMJ is the point of contact between a nerve fiber and a muscle; an action potential initiates action potential and causes ACh release at NMJ which then crosses the synapse to attach to receptors and depolarize the muscle causing contraction. Antiacetylcholine receptor antibodies (AChR-Abs) have been found in up to 40 to 77% of patients with OMG which reduce the number of receptors by receptor blockade.[4] Increased susceptibility of extraocular muscles (EOMs) to myasthenia is due to unique structural and functional properties compared to other striated muscles. EOMs have decreased AChR receptors and decreased post-synaptic folding.[6] EOMs express both the adult ($\alpha 2\beta\varepsilon\delta$) and the embryonic ($\alpha 2\beta\gamma\delta$) isoforms of the AChR.[7] The functional characteristics of fetal AChR may harbor susceptibility to myasthenia gravis. Fetal AChR has a longer open time and higher affinity for agonists.

OMG usually presents with painless diplopia or ptosis with intact pupillary reflexes. Fatigability, fluctuations, and relapsing

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remitting course often corroborates the diagnosis. Weakness of the orbicularis oculi is uncommon at presentation but is often seen later in the course.[8] The involvement is asymmetrical and usually has a fluctuating course, and may shift from one eye to another. Complete ophthalmoplegia is seen in chronic cases. Clinical features are similar in AChR positive and double seronegative (dsN) patients. In patients positive for muscle-specific kinase (MuSK), Abs ocular symptoms tend to be less prominent, often causing symmetrical gaze limitations with transitory diplopia and bilateral, largely symmetrical, ptosis.[9] Medial rectus is the most commonly affected EOM followed by the superior rectus. Patients with OMG may exhibit hypometric large saccades and hypermetric small saccades, which may be a consequence of CNS adaptation to EOM weakness. Pupillary examination is, usually, normal, and this serves as a useful tool to distinguish OMG from conditions such as pupil involving third nerve palsy, Horner's syndrome, and botulism. Pupillary abnormalities rarely have been in OMG, mentioned to fatigue of accommodation.[10–12]

Diagnosis

Diagnosis is done by clinical examination, few specific clinical tests, pharmacological tests, serological tests, and electrophysiological tests.

Clinical Tests

Two commonly used tests in the clinic are the rest or sleep test and the ice test. The ice test is done by keeping gloves filled with crushed ice over the eyelid with ptosis in unilateral ptosis or both eyelids in bilateral ptosis for 2 minutes. A confirmed improvement of the ptosis has to be documented for the test to be positive. The ice test is 90% sensitive and 100% specific in OMG and is more useful in the setting of ptosis but less accurate in ophthalmoplegia.[13] The sleep test measures the improvement in manifestations of OMG after a period of rest. The patient takes rest with closed eyes for 30 minutes. Prior to the test, the patient is examined, and the ocular motility deficits and/or ptosis present are measured. After a 30-minute period of sleep, if the deficits improve a diagnosis of OMG is made. Reappearance of the myasthenic signs over the next 30 seconds to 5 minutes further reinforces the diagnosis.[13,14]

Pharmacological Testing and Laboratory Investigations

With the advent of newer and sophisticated modalities like serological testing and advanced electrophysiology, the earlier popular diagnostic tests by using pharmacological agents are now usually not done. Edrophonium and neostigmine are two pharmacological agents which were used to diagnose OMG. Edrophonium competitively inhibits the acetylcholinesterase at the NMJ, thereby preventing the breakdown of ACh. This results in an increase in synaptic ACh, providing maximum saturation of the limited available receptor population in myasthenia. Ptosis and ocular deficits are measured and photographically recorded before initiation of edrophonium. Then edrophonium is injected intravenously in an appropriate dose, and onset of effect usually begins 30 to 60 seconds after injection. The dose of edrophonium chloride is 0.10 mg/kg in children and 10 mg or less in adults and 0.05 to 1.0 mg (subcutaneously) in infants. Edrophonium may cause serious side effects due to the increased muscarinic activity—like lacrimation, abdominal cramping, salivation, and sweating. Life-threatening side effects include bradycardia, bronchospasm, and hypotension; the test should be carried out in a guarded setting with continuous monitoring of vitals and atropine should be readily available. The sensitivity of the test is 95% in GMG and about 86% for OMG.[15–17]

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Neostigmine is a longer-acting AChE inhibitor and onset of action is usually after 30 minutes of intramuscular injection and the duration of action is longer. The usual dose for adults is 1.5 mg in deep intramuscular over deltoid muscle. The longer duration of action provides more time for a detailed examination and analysis. However, the patient should be cautioned regarding the potential muscarinic side effects, which are less than edrophonium.[4]

Serological Testing

Anti-Acetylcholine Receptor (AChR) Antibodies

Anti-acetylcholine receptor (AChR) antibodies are the most commonly used serological test in diagnosing OMG. Although the AChR antibody assay is very sensitive (80–90%) in GMG, it is classically thought to be less sensitive in OMG, with reported seropositivity ranging between 40 and 70%.[18] Increased sensitivity of radio-immunoassays and the availability of the newer cell-based assays in recent years have contributed to the higher sensitivity of the assay. Few studies have attributed to the higher presentation in the older age group over the last two decades. There are three types of AChR antibodies: binding, modulating, and blocking. The binding AChR antibody is the most useful for diagnostic testing because of its higher seropositivity.[19–21]

Anti-Muscle-Specific Kinase (MuSk) Antibodies

Anti-MuSk antibodies are rare in isolated OMG. It has been reported in 38 to 50% of patients who are negative for AChR antibodies.[22]

Other Autoantibodies (Low-Density Lipoprotein Receptor–Related Protein 4, Cortactin, Agrin)

In cases of double-seronegative myasthenia gravis (dsNMG), in which both AChR and MuSK antibodies are negative, there is possibility of presence of low-density lipoprotein receptor–related protein 4 (LRP4) and other autoantibodies to other components of the post-synaptic apparatus. The frequency of positive LPR4 in dsNMG ranges from 2 to 50% across different studies. dsNMG with positive LPR4 antibodies is seen in young females, is frequently mild with isolated ocular symptoms, and typically responds well to pyridostigmine or prednisone. LPR4 antibodies are also positive with other neurologic disorders such as polymyositis, neuromyelitis optica, multiple sclerosis, and amyotrophic lateral sclerosis.[23–25]

Electrophysiologic Tests

In the diagnosis of OMG both repetitive nerve stimulation (RNS) studies and single-fiber electromyography (SFEMG) are recommended.[26]

RNS Study

After stimulating the targeted nerve electrically 6 to 10 times at 2 to 3 Hz (slow rate) with a supramaximal stimulus, the compound muscle action potential (CMAP) is recorded. In myasthenia gravis due to decrease in muscle fiber action potential, CMAP decreases in both amplitude and area and a characteristic decrement (>10%) in muscle action potential amplitude is typically seen by the fourth or fifth response in a series of low-frequency RNS, whereas the amplitude remains the same in normal individuals. However, in pure OMG, this decrement is seen in only 33% of the patients.[27,28]

Single-Fiber Electromyography (SFEMG)

Single-fiber electromyography (SFEMG) is the most sensitive diagnostic test for detecting abnormal neuromuscular transmission. In SFEMG, we use a specialized concentric needle to record individual muscle fiber action potentials with the help of 500-Hz high-frequency filter and 25-µm diameter recording surface. The variance of the stimulus to response is the neuromuscular jitter. SFEMG has a sensitivity

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of 85 to 100% for OMG when used on the frontalis or orbicularis oculi muscle.[29]

When both ice pack and SEFMG tests were positive, the sensitivity for OMG diagnosis increased to 82% and the specificity to 92%, with a negative predictive value of 94%. Therefore, when both tests are negative, the diagnosis of OMG becomes extremely unlikely.[30]

Imaging Studies

As many as 70% of patients with myasthenia may have thymic hyperplasia, and 10 to 15% may harbor a thymoma. Computed tomography (CT) of the chest is advised in patients diagnosed with myasthenia to detect this association.[31]

Treatment of OMG

Most of the randomized controlled trials on the treatment of myasthenia gravis are for GMG and hence the treatment of OMG lacks evidence. The most commonly used medical treatment agents are cholinesterase inhibitors (pyridostigmine), oral steroids, second-line immunosuppressive agents (azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus), in acute cases intravenous immunoglobulins, and plasma exchange, and biologic monoclonal antibody therapy—eculizumab and rituximab. Surgical treatment includes thymectomy, ptosis repair, or strabismus surgery in stable ptosis and diplopia cases. In pure OMG, treatment by immunomodulators other than steroids may not be required; however, there is lack of consensus.[32]

Acetylcholinesterase inhibitors can serve to increase the duration of action of the neurotransmitter. These provide symptomatic improvement only and has no effect on the immunological basis of the disease. Pyridostigmine is the prototype that is used, and it works better on ptosis than diplopia. In tablet form (30 mg), it is, usually, administered two to four times a day, up to a maximum of 1500 mg/day. It is contraindicated in patients with asthma and cardiac arrythmias. Acetylcholinesterase inhibitors do not influence the natural course of the disease (36% of patients with OMG who were treated with pyridostigmine and not steroids developed GMG within 2 years).[33,34]

Corticosteroids are the most commonly used immunomodulators in patients with myasthenia gravis. They primarily act through their anti-inflammatory properties, also causing a reduction in cytokine expression, lymphocyte differentiation and proliferation, and increase in muscle AChR synthesis.[35] Steroid initiation should not be done in high doses as it may lead to worsening, rather it should be started slowly, gradually to a level of 1 mg/kg/day, continued over 6 to 12 weeks, and then tapered over months.[36] Corticosteroids produce favorable response in OMG in 66 to 85% of patients. With only corticosteroids patients rarely go into remission. Steroids in the course of early OMG reduce the likelihood of progression to GMG (according to some studies, from a rate of 36 to 83% in patients without prednisolone to 7 to 17% of patients treated with prednisolone). Prednisone may also delay generalization. Without prednisone, GMG develops in 50% of OMG patients, typically within 1 year.[34,37] Common long-term side effects of steroids are hypertension, diabetes, obesity, loss of bone density, and hormonal imbalance.

Immunosuppressive Therapy

Azathioprine, which is a purine antagonist that inhibits DNA and RNA synthesis in fast dividing T- and B-cells, can be used both as monotherapy (e.g., in steroid-resistant patients) as well as in conjunction with oral corticosteroids. The latter modality has been shown in randomized controlled trials to have a steroid-sparing effect and is associated with fewer failures and longer remissions.[38] The clinical response to azathioprine alone is, usually,

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delayed (>6 months), and is accompanied by a progressive fall in AChR-Ab titers. The full effect is seen after 2 to 3 years of continuous administration. There are serious side effects like hepatotoxicity and bone marrow toxicity and blood counts and liver function tests should be done bi-weekly for the first 2 months after initiating treatment and monthly thereafter. Treatment should be stopped if the white blood cells count falls below 3000/mm^3. Cyclosporine A is a third-line drug inhibiting calcineurin, which decreases the antigen-stimulated interleukin-2 production in T-cells and may be of particular use in patients who are dependent or intolerant of steroids and/or azathioprine. Treatment is initiated at a dose of 5 mg/kg/day in two to three divided doses and is subsequently modified. Serious side effects include renal failure and less serious side effects include hirsutism, gingival hyperplasia, gastrointestinal disturbance, flu-like syndrome, myalgia, and hypertension. Mycophenolate mofetil (MMF) selectively inhibits T- and B-lymphocyte proliferation by blocking purine synthesis. It is administered orally in a dose of between 1000 and 1500 mg twice a day and with fewer side effects than azathioprine. It helps in alleviating symptoms when used in adjunct with low-dose steroids.[39–43]

OMG may not respond to steroids, and about 20% of patients may develop treatment-resistant ophthalmoplegia. MuSK antibodies are predominantly IgG4 and less effective in activating the complement pathway. Therefore, complement inhibitors can be effective in AChR myasthenia but are expected to be less effective in MuSK myasthenia.[44] Patients who fail steroid treatment or develop significant adverse effects should be offered second-line immunosuppressive agents, such as mycophenolate mofetil, azathioprine, cyclosporine, cyclophosphamide, or tacrolimus. Rituximab (anti-CD20) has been used in refractory myasthenia, particularly in MuSK myasthenia.[45,46]

Thymectomy is often considered as the treatment of choice in GMG but in OMG the role of thymectomy is controversial and is thought to be nonsuperior to adequate medical management. A recent nonrandomized series found that age below 40 years was the only independent prognostic factor significantly associated with complete remission of OMG in patients who underwent thymectomy.[47] AChR-Ab+ patients with OMG who do not respond adequately to acetylcholinesterases and who either prefer not to take immunosuppressive therapy or have contraindications to or are refractory to immunosuppressive agents may be offered thymectomy as per the International Consensus Guidance for Management of Myasthenia Gravis, 2020.[48]

Risk of Progression to GMG

The reported range of conversion to GMG varies between 20 and 85% across different studies.[1] Some studies required that patients should have only ocular symptoms for at least 3 months to be considered true OMG and reported a conversion rate of 21.1% among all patients at an average of 4 years after diagnosis and a lower rate of conversion (13.7%) if seronegative for AChR and MuSK antibodies. Predictors for generalization of OMG include AChR seropositivity and high AChR titer, thymoma or thymic hyperplasia, age over 50, abnormal RNS, and severity of symptoms.[3] Evidence of reducing the risk of generalization of OMG by treatment with immunosuppression (steroids) is derived only from retrospective studies, and no randomized controlled trials have addressed this so far.[49] A multicenter retrospective study to create a prognostic score to predict the risk of conversion of OMG into GMG found that AChR seropositivity, presence of comorbidities, and thymic hyperplasia were independently associated with increased generalization rates of OMG. It is important to identify patients

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with higher risk of conversion to GMG and they should be treated aggressively.

Conclusion

There is lack of consensus guidelines on OMG, specifically regarding therapeutic options. However, it is evident from literature that OMG should be diagnosed accurately, and early treatment should be initiated to prevent conversion into GMG. However, further studies and good-quality randomized controlled trials are required to fulfill the unmet needs in the treatment of myasthenia gravis.

Case Vignette 1

A 6-year-old girl presented in our clinic with drooping of right eyelid, which was noticed by the parents after a trivial infection which was followed by bilateral ptosis after 7 days. There was diurnal fluctuation and fatiguability. There was no muscle weakness, no bulbar symptoms, and no nasal intonation in speech. The child presented with only ocular symptoms. After evaluation and investigation RNST was found to be inconclusive as the child did not cooperate much. AChR antibodies were positive, and CECT of chest was unremarkable. The child was also genetically screened, and was found negative for congenital myasthenia syndromes. The child was treated successfully with low-dose steroid, which was stopped later and pyridostigmine was given. The child is currently doing well (**Fig. 27.1**).

Fig. 27.1 A 6-year-old girl presented with bilateral ptosis. She was treated with low-dose steroid and pyridostigmine.

Case Vignette 2

A 43-year-old female patient presented to another hospital 5 years ago with bilateral ptosis. She was evaluated and some management was started, which was stopped by them after 1 year. After 3 years she again started having diplopia and ptosis, and this time, she developed proximal weakness as well, and difficulty in getting up the stairs. Also, she had fatiguability and diurnal variation. However, she was treated with alternative medicines and 2 months back she attended ER of our hospital with difficulty in breathing, nasal intonation, and difficulty in eating and swallowing. Eventually, she was treated for myasthenic crisis and received ventilatory support for 7 days. She was treated with plasma exchange followed by immunomodulators. Her AChR antibodies were strongly positive. Currently, she is doing well on immunomodulators and pyridostigmine and has been planned for thymectomy (**Fig. 27.2a, b**).

Consents have been taken from patients for publication.

Fig. 27.2 A 43-year-old female patient with bilateral ptosis. She was treated with plasma exchange followed by immunomodulators and then thymectomy.

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References

1. Hendricks TM, Bhatti MT, Hodge DO, Chen JJ. Incidence, epidemiology, and transformation of ocular myasthenia gravis: a population-based study. Am J Ophthalmol 2019;205:99–105
2. Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. J Neurol Neurosurg Psychiatry 1998;65(4):492–496
3. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest 2006;116(11):2843–2854
4. Grigg J. Extraocular muscles: relationship of structure and function to disease. Aust N Z J Ophthalmol 1999;27(6):369–370
5. Singhal BS, Bhatia NS, Umesh T, Menon S. Myasthenia gravis: a study from India. Neurol India 2008;56(3):352–355
6. Liu R, Xu H, Wang G, et al. Extraocular muscle characteristics related to myasthenia gravis susceptibility. PLoS One 2013;8(2):e55611
7. Spencer RF, Porter JD. Biological organization of the extraocular muscles. Prog Brain Res 2006;151: 43–80
8. Cleary M, Williams GJ, Metcalfe RA. The pattern of extra-ocular muscle involvement in ocular myasthenia. Strabismus 2008;16(1):11–18
9. Evoli A, Alboini PE, Iorio R, Damato V, Bartoccioni E. Pattern of ocular involvement in myasthenia gravis with MuSK antibodies. J Neurol Neurosurg Psychiatry 2017;88(9):761–763
10. Yee RD, Cogan DG, Zee DS, Baloh RW, Honrubia V. Rapid eye movements in myasthenia gravis. II. Electro-oculographic analysis. Arch Ophthalmol 1976;94(9):1465–1472
11. Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. Neurology 1987;37(8): 1383–1385
12. Manson N, Stern G. Defects of near vision in myasthenia gravis. Lancet 1965;1(7392):935–937
13. Kubis KC, Danesh-Meyer HV, Savino PJ, Sergott RC. The ice test versus the rest test in myasthenia gravis. Ophthalmology 2000;107(11):1995–1998
14. Odel JG, Winterkorn JM, Behrens MM. The sleep test for myasthenia gravis. A safe alternative to Tensilon. J Clin Neuroophthalmol 1991;11(4):288–292
15. Kaminski HJ, Maas E, Spiegel P, Ruff RL. Why are eye muscles frequently involved in myasthenia gravis? Neurology 1990;40(11):1663–1669
16. Barton JJ, Fouladvand M. Ocular aspects of myasthenia gravis. Semin Neurol 2000;20(1):7–20
17. Phillips LH II, Melnick PA. Diagnosis of myasthenia gravis in the 1990s. Semin Neurol 1990;10(1): 62–69
18. Vincent A, Newsom Davis J. Anti-acetylcholine receptor antibodies. J Neurol Neurosurg Psychiatry 1980;43(7):590–600
19. Peeler CE, De Lott LB, Nagia L, Lemos J, Eggenberger ER, Cornblath WT. Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. JAMA Neurol 2015;72(10): 1170–1174
20. Ding J, Zhao S, Ren K, et al. Prediction of generalization of ocular myasthenia gravis under immunosuppressive therapy in Northwest China. BMC Neurol 2020;20(1):238
21. Behbehani R, Ali A, Al-Moosa A. Ocular myasthenia: clinical course and the diagnostic utility of assaying acetylcholine receptor antibodies. Neuroophthalmology 2022;46(4):220–226
22. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 2001;7(3):365–368
23. Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol 2011;69(2):418–422
24. Bacchi S, Kramer P, Chalk C. Autoantibodies to low-density lipoprotein receptor-related protein 4 in double seronegative myasthenia gravis: a systematic review. Can J Neurol Sci 2018;45(1):62–67
25. Zouvelou V, Zisimopoulou P, Rentzos M, et al. Double seronegative myasthenia gravis with anti-LRP 4 antibodies. Neuromuscul Disord 2013;23(7): 568–570
26. Katzberg HD, Bril V. A comparison of electrodiagnostic tests in ocular myasthenia gravis. J Clin Neuromuscul Dis 2005;6(3):109–113
27. Ozdemir C, Young RR. The results to be expected from electrical testing in the diagnosis of myasthenia gravis. Ann N Y Acad Sci 1976;274: 203–222
28. Costa J, Evangelista T, Conceição I, de Carvalho M. Repetitive nerve stimulation in myasthenia gravis—relative sensitivity of different muscles. Clin Neurophysiol 2004;115(12):2776–2782
29. Padua L, Stalberg E, LoMonaco M, Evoli A, Batocchi A, Tonali P. SFEMG in ocular myasthenia gravis diagnosis. Clin Neurophysiol 2000;111(7): 1203–1207

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30. Giannoccaro MP, Paolucci M, Zenesini C, et al. Comparison of ice pack test and single-fiber EMG diagnostic accuracy in patients referred for myasthenic ptosis. Neurology 2020;95(13): e1800–e1806
31. Osserman KE, Tsairis P, Weiner LB. Myasthenia gravis and thyroid disease: clinical and immunologic correlation. J Mt Sinai Hosp N Y 1967; 34(5):469–483
32. Cornblath WT. Treatment of ocular myasthenia gravis. Asia Pac J Ophthalmol (Phila) 2018;7(4): 257–259
33. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. Arch Neurol 2003; 60(2):243–248
34. Kupersmith MJ, Moster M, Bhuiyan S, Warren F, Weinberg H. Beneficial effects of corticosteroids on ocular myasthenia gravis. Arch Neurol 1996;53(8):802–804
35. Finelli PF, Hoyt WF. Myasthenic abduction mystagmus in a patient with hyperthyroidism. Neurology 1976;26(6 PT 1):589–590
36. Gandhi RA, Nair AG. Ocular myasthenia gravis. In: Chaudhari Z, Vanathi M, eds. Postgraduate Ophthalmology. New Delhi: Jaypee Brothers Medical Publishers; 2011:1510–1521
37. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984;15(3): 291–298
38. Palace J, Newsom-Davis J, Lecky B; Myasthenia Gravis Study Group. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Neurology 1998;50(6): 1778–1783
39. Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann N Y Acad Sci 1993;681: 539–551
40. Tindall RS, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. N Engl J Med 1987;316(12):719–724
41. Chan JW. Mycophenolate mofetil for ocular myasthenia. J Neurol 2008;255(4):510–513
42. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 2008;71(6): 394–399
43. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 2008;71(6):400–406
44. Heckmann JM, Nel M. A unique subphenotype of myasthenia gravis. Ann N Y Acad Sci 2018; 1412(1):14–20
45. Di Stefano V, Lupica A, Rispoli MG, Di Muzio A, Brighina F, Rodolico C. Rituximab in AChR subtype of myasthenia gravis: systematic review. J Neurol Neurosurg Psychiatry 2020;91(4):392–395
46. Menon D, Barnett C, Bril V. Novel treatments in myasthenia gravis. Front Neurol 2020;11:538
47. Liu X, Zhou W, Hu J, et al. Prognostic predictors of remission in ocular myasthenia after thymectomy. J Thorac Dis 2020;12(3):422–430
48. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology 2021;96(3):114–122
49. Galassi G, Mazzoli M, Ariatti A, Kaleci S, Valzania F, Nichelli PF. Antibody profile may predict outcome in ocular myasthenia gravis. Acta Neurol Belg 2018;118(3):435–443

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28 Should Thymectomy Be Done in All Patients with Myasthenia Gravis?

Vishnu V. Y.

Introduction

The utility of thymectomy was identified serendipitously in the early part of the last century when Sauerbruch et al performed thymectomy accidentally along with thyroidectomy in a patient with both Graves' disease and myasthenia and noted significant improvement in weakness.[1] Later, Blalock et al showed more evidence in the 1940s by removing thymus first from a myasthenia gravis (MG) patient with thymoma and later from MG patients with normal thymus.[2] Larger observational series with longer follow-ups reported significant improvement in weakness post thymectomy in adults and children.[3–5] The American Academy of Neurology (AAN) practice parameter in 2000 concluded that the quality of evidence was poor and thymectomy may be considered an option for MG patients without thymoma.[6] For patients with thymoma, irrespective of MG status, National Comprehensive Cancer Network (NCCN) guidelines recommend thymectomy as the standard of care.[7] In 2016, a landmark phase 3 randomized controlled trial was completed, which compared thymectomy plus prednisone versus prednisone alone in acetylcholine receptor auto-antibody-positive (ACHR Ab+) MG patients.[8] The trial results prompted a change in MG practice parameters and guidelines worldwide.

In this chapter, we will look at the evidence regarding the role of thymectomy in MG and discuss whether "thymectomy should be done in all patients with MG."

Controversial Issues Regarding Thymectomy in MG

The major contentious issues regarding thymectomy in MG are:

- Should thymectomy be advised in late-onset MG (age >50 years)?
- Thymectomy in ocular MG with and without AChR Ab+.
- Type and extent of surgery in thymectomy.
- Seronegative and other antibody-positive MG.
- Health consequences of thymus removal in adults.

Evidence Base for Thymectomy in Myasthenia Gravis

Currently, thymectomy is advised in two groups of MG patients:

- Generalized MG with AChR antibodies (age < 50 years).
- Thymoma.

Clinical scenarios where thymectomy is individualized due to lack of high-quality evidence:

- AChR Ab+ ocular MG.
- Age 50 to 65 years.

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- Longer disease duration.
- Small and slow-growing thymomas in elderly and frail MG patients.
- Seronegative MG.

Before 2016, there was good observational data, even with their inherent bias, to support the use of thymectomy in generalized MG with AChR antibodies starting from the 1966 MGH-Mt Sinai combined cohort of 1335 MG patients.[9] This was supported by the well-documented role of thymus in AChR-MG. But these were retrospective series or cohorts with or without nonrandomized controls.

MGTX trial was an international multicenter randomized trial conducted on AChR Ab+ generalized non-thymomatous MG (MGFA II–IV) with <5 years disease duration, comparing extended transsternal thymectomy + prednisolone with alternate-day prednisolone alone.[8] Patients with thymoma or age >65 years were excluded from the study. Prednisone was initiated after randomization and was titrated up to 100 mg (alternate days) or 1.5 mg/kg, whichever was lower. In those patients who were already receiving steroids, a maximum dose of 120 mg was allowed to attain minimal manifestation (MM) status (no symptoms +/− minor signs). Surgery was done within 30 days of initiation of steroids, and the blinded outcome assessor started tapering steroids after 4 months as per the protocol to maintain the MM status. Azathioprine was added in those who failed to achieve MM status at 1 year or who had unacceptable side effects. The two co-primary outcomes were the weighted average quantitative myasthenia gravis (QMG) score and time weighted average dose of required prednisolone over 3 years duration. After screening 6958 persons in 18 countries (majority were from the USA), 231 patients were found eligible, and 126 were recruited. At 36 months, the primary outcome scores clearly indicated that thymectomy enhanced the QMG score by 2.84 (6.15 vs. 8.99), 2.3-point reduction being clinically significant and lower requirement of steroids. The secondary outcomes also favored thymectomy, including the requirement for azathioprine, hospitalization for exacerbations, and more participants with MM status.

MGTX trial provided class I evidence for the role of thymectomy in the management of AChR Ab+ generalized non-thymomatous MG. However, there were some limitations in this study, mainly the high dose of steroids used, which is not the usual clinical practice, and lack of concomitant steroid-sparing immunosuppressant.[10] The trial used extended trans-sternal thymectomy, which removes almost 85 to 95% of thymic tissue. But whether this can be extrapolated to minimally invasive surgeries is a dilemma.[11]

The long-term data (2-year extension data) of the trial (total of 5 years) was also published 3 years later.[12] The benefits of thymectomy persisted at 5 years, and there were reductions in mean QMG scores and alternate-day prednisone doses. There was also an increase in the proportion of patients reaching the MM status. In the MGTX trial, the beneficial effects of thymectomy in patients >50 years of age were not as robust. Even in the extension phase, this ambiguity persisted.

International Consensus Guidance for Management of Myasthenia Gravis (2020)[13] has given the following recommendations regarding thymectomy:

- "*In non-thymomatous, generalized MG patients with AChR-Ab, aged 18–50 years, thymectomy should be considered early in the disease to improve clinical outcomes and to minimize immunotherapy requirements and the need for hospitalizations for disease exacerbations*
- *Thymectomy should be strongly considered in patients with AChR-Ab+ generalized MG if they fail to respond to an initial adequate trial of immunotherapy or have intolerable side effects from that therapy*

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- *Thymectomy for MG is an elective procedure and should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function.*"

Surgical Procedure

The classical method of thymectomy (technique used in the MGTX trial as well) is extended transsternal thymectomy, which completely removes thymus and fat. The main goal is to remove maximum thymic tissue and preserve vital structures like the vagus, phrenic, and recurrent laryngeal nerve.

Minimally invasive surgeries used now are video-assisted thoracoscopic thymectomy (VATS) or robotic-assisted thoracoscopic surgery. Both have a higher risk of leaving residual thymic tissue. There is no good-quality RCT and it may be challenging to extrapolate the open surgery effects.[10,11]

International Consensus Guidance for Management of Myasthenia Gravis (2020)[13] has given the following recommendations regarding surgical options for thymectomy:

> "*Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches.*"

Seronegative MG

There is a lack of evidence to ascertain the role of thymectomy in AChR Ab− patients. Thymectomy may be considered if they fail to respond to conventional immunosuppressive therapy.

Ocular MG

There are considerable retrospective observational studies examining the role of thymectomy in ocular MG. A systematic review and meta-analysis looked at 26 studies with 640 patients, and the pooled CSR rate was 0.5074 (95% CI, 0.4196–0.5947) with significant heterogeneity.[14] Subgroup analysis showed variable efficacy based on geographical location and better outcomes in children. Only a good-quality RCT can solve the clinical problem of equipoise.

International Consensus Guidance for Management of Myasthenia Gravis (2020)[13] has given the following recommendations regarding thymectomy in ocular MG:

> "AChR-Ab+ patients with ocular MG who do not respond adequately to acetylcholinesterases and who either prefer not to take IS therapy or have contraindications to or are refractory to IS agents may be offered thymectomy."

Health Consequences of Thymus Removal in Adults[15,16]

The thymus is crucial for T-cell maturation, which guarantees a strong response against foreign antigens while maintaining self-tolerance. Natural thymic involution occurs during life due to ageing, and it was presumed that the thymus did not play a significant role in adulthood due to its involution. But new evidence challenges this concept, as studies are showing that thymopoiesis existing in adulthood can have a positive impact, while its decline may increase the risk of malignancy and autoimmune diseases. This has raised concerns that thymectomy done for various indications in adulthood may have deleterious health consequences.

Kooshesh et al published a retrospective observational study involving 1146 patients

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who had thymectomy and were matched with those who had cardiothoracic surgery without thymectomy.[16] The study showed that patients with thymectomy had an elevated risk of all-cause death, autoimmune disease, and malignancy. In the first 2 years, there was twofold increase in death and development of malignancy. But there were several methodological issues with this study. Thymoma or suspicion of thymic mass was the indication for thymectomy in 871/1146 patients in the study. The increased mortality and malignancy in the thymectomy group may be related to pre-existing thymus issues itself rather than thymectomy.[15] Moreover, in the study, only 265 patients had other indications for thymectomy, like parathyroid or thyroid surgeries, cardiac surgery, or other indications of thymectomy. In these scenarios, a complete thymectomy is usually not performed. Cervical extensions of the thymus are usually not excised during cardiac surgery. The increased death in the thymectomy group may be due to selection bias.

Various studies have shown unambiguous benefits of thymectomy in AChR Ab+ MG and those with thymoma. Hence, based on our current knowledge that the thymus plays an immunologic role throughout life, avoiding "unnecessary" thymectomy during cardiac surgery or benign cysts or hyperplasia of the thymus (without MG) may be wise. However, the risk–benefit ratio of thymectomy in thymic malignancy and AChR Ab+ MG is unequivocally in favor of thymectomy.

Conclusion

As per the currently available evidence, extended transsternal thymectomy is recommended for all patients with thymoma (with or without MG) and AChR Ab+ generalized MG (age <50 years). Other minimally invasive surgical procedures probably work as good as the conventional procedure, but there is a lack of high-quality evidence. The health consequences of removal of the thymus in adults are more in favor of thymectomy in patients with thymoma and AChR Ab+ MG compared to incidental removal of the thymus during cardiac surgeries or for benign cysts. Evidence for thymectomy in AChR Ab+ ocular MG and seronegative MG is lacking, and based on observational data, thymectomy may be considered if they are refractory to immunosuppressants.

References

1. Hughes T. The early history of myasthenia gravis. Neuromuscul Disord 2005;15(12):878–886
2. Blalock A, Harvey AM, Ford FR, Lilienthal JL. The treatment of myasthenia gravis by removal of the thymus gland: preliminary report. JAMA 1941; 117(18):1529–1533
3. Eaton LM, Clagett OT, Bastron JA. The thymus and its relationship to diseases of the nervous system; study of 374 cases of myasthenia gravis and comparison of 87 patients undergoing thymectomy with 225 controls. Res Publ Assoc Res Nerv Ment Dis 1953;32:107–124
4. Buckingham JM, Howard FM Jr, Bernatz PE, et al. The value of thymectomy in myasthenia gravis: a computer-assisted matched study. Ann Surg 1976;184(4):453–458
5. Rodriguez M, Gomez MR, Howard FM Jr, Taylor WF. Myasthenia gravis in children: long-term follow-up. Ann Neurol 1983;13(5):504–510
6. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55(1):7–15
7. NCCN guidelines thymomas and thymic carcinomas. Accessed July 25, 2024 at: nccn.org/professionals/physician_gls/pdf/thymic.pdf
8. Wolfe GI, Kaminski HJ, Aban IB, et al; MGTX Study Group. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375(6): 511–522
9. Cooper JD. History of thymectomy for myasthenia gravis. Thorac Surg Clin 2019;29(2):151–158
10. Berrih-Aknin S, Le Panse R. Thymectomy in myasthenia gravis: when, why, and how? Lancet Neurol 2019;18(3):225–226

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11. Sussman J. Thymectomy: the more you know, the more you know you don't know. Pract Neurol 2016;16(6):426–427
12. Wolfe GI, Kaminski HJ, Aban IB, et al; MGTX Study Group. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. Lancet Neurol 2019;18(3):259–268
13. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology 2021;96(3):114–122
14. Zhu K, Li J, Huang X, et al. Thymectomy is a beneficial therapy for patients with non-thymomatous ocular myasthenia gravis: a systematic review and meta-analysis. Neurol Sci 2017;38(10): 1753–1760
15. Kaminski HJ, Kusner LL, Cutter GR, et al. Does surgical removal of the thymus have deleterious consequences? Neurology 2024;102(12):e209482
16. Kooshesh KA, Foy BH, Sykes DB, Gustafsson K, Scadden DT. Health consequences of thymus removal in adults. N Engl J Med 2023;389(5): 406–417

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29 Comprehensive Stroke Center—Challenges and Lessons Learned

Vijaya Pamidimukkala and Y. Yelamanchi Ramachandra Prasad

Background/Gaps in Stroke Care

Stroke is a leading cause of death and disability across the world and two-thirds of death occurring in the lower and middle income countries. In India 1.8 million people suffer from stroke annually[1] and every minute 3 people develop stroke. According to the ICMR, stroke was India's 4th leading cause of death and 5th leading cause of disability-adjusted life years (DALYs) in 2016 (MoHFW, Government of India).[1] Case fatality rates in 1 month range from 18 to 42%. This is in contrast to the dismal rate (<1%) of thrombolysis for stroke. There are many evidence-based effective treatments now extending up to 24 hours of stroke onset! With proper awareness and planning, stroke can be a highly preventable and treatable disease. Ideal management of stroke should optimize the continuum of care starting from prevention of stroke, recognition of onset of acute event, prehospital care, hyperacute phase, acute inpatient care, stroke rehabilitation, prevention of recurrent stroke, and concluding with community reintegration and long-term recovery.

But there is a huge gap in the availability of stroke care services across India. The World Stroke Organization (WSO) in its Global Stroke Action Plan Guidelines talks about a model that categorizes the availability of stroke services globally into three levels[2]:

- Access to minimum health care services.
- Access to essential stroke services.
- Access to advanced stroke services.

The Beginning of Organized Stroke Care

Time is brain in case of stroke management and every minute counts. Stroke units are the first successful intervention.[3] Cochrane Review 2013 study showed that stroke patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living at home 1 year after the stroke.[4] Since then stroke units have become established as the central component of modern stroke services.[5] The positive effect of stroke unit is replicated in low and middle income countries.[6]

Stroke care has substantially evolved during the past several decades. The results of clinical trials of acute stroke care, advanced treatment including interventional endovascular therapies, minimally invasive neurosurgical management, and multidisciplinary rehabilitation services have led to new evidence-based options for care of stroke patients. One of the major advancements in stroke is the organization of care which has and is being transformed by primary and comprehensive stroke centers—which led to cost-effective and better outcomes.

Importance of Stroke Centers

The next milestone in stroke management is the establishment of stroke systems of care.[7] To deliver all these evidence-based treatments for the needy patients we need to develop systems of care.

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Brain Attack Coalition (BAC)

A group with representatives from major professional advocacy and organizations involved in stroke center formed the concept of stroke centers and initially proposed two types—primary and comprehensive.[8] A primary stroke center (PSC) has the necessary staffing, infrastructure, and programs to stabilize and treat most of the acute stroke patients including intravenous (IV) thrombolysis, stroke unit care, and secondary prevention. Although PSCs provide stroke patients with high-quality care, some patients with complex stroke types, severe deficits, or multiorgan disease may require and benefit from specialized care and technological resources not available in a typical PSC. Such patients often require advanced diagnostic and treatment procedures directed by specially trained physicians and other health care professionals.

After 10 years of experience with PSCs, the concept of comprehensive stroke center was formed. A comprehensive stroke center (CSC) is defined as a facility or system with the necessary personnel, infrastructure, expertise, and programs to diagnose and treat stroke patients who require a high intensity of medical and surgical care, specialized tests, or interventional therapies. Additional functions of a CSC would be to act as a resource center for other facilities in its region such as PSCs or acute stroke ready hospitals (ASRHs). The BAC has established recommendations for the development of CSCs.[9]

Evidence to Support the Value of Comprehensive Stroke Centers

A nationwide observational study from Finland showed that patient outcomes were better in stroke centers fulfilling standardized BAC criteria than a hospital without stroke centers. Patients treated in stroke center hospitals have lower mortality and less institutional care at 1 year of stroke as well as during entire follow-up of up to 9 years. In a registry linkage study from Finland the number needed to treat to prevent one death on institutional care for 1 year was 29 per CSC versus 40 per PSC.[10]

Components of CSC

Ideal foundational requirements for CSCs[11]:

- Stroke program leadership.
- Personnel resources.
- Neuroimaging capabilities.
- Neuro-procedural and neuro-intervention capabilities.
- Neurosurgical and critical care setup.
- Hospital bed resources.
- Policies, processes, and protocols.
- Continuous quality improvement.
- Stroke registry and clinical research.
- Educational resources for community, staff, and physicians.

Stroke Program Leadership

A CSC is expected to provide the highest possible level of acute stroke care as well as to optimize all the components in the continuum of care from prehospital to rehabilitation and reintegration into the society. It requires significant commitment from the hospital administration as well as a dedicated team working under respective leaders (**Fig. 29.1**).

Stroke Program Medical Director (SPMD)

SPMD should be experienced and knowledgeable to serve as the leader, directing the program policies and procedures to optimize performance and quality metrics, delivering formal and informal education, planning and executing stroke community education, performing gap analysis, and planning for improvement when required as well as conducting Institutional Ethics Committee approved clinical research and maintaining stroke data base.

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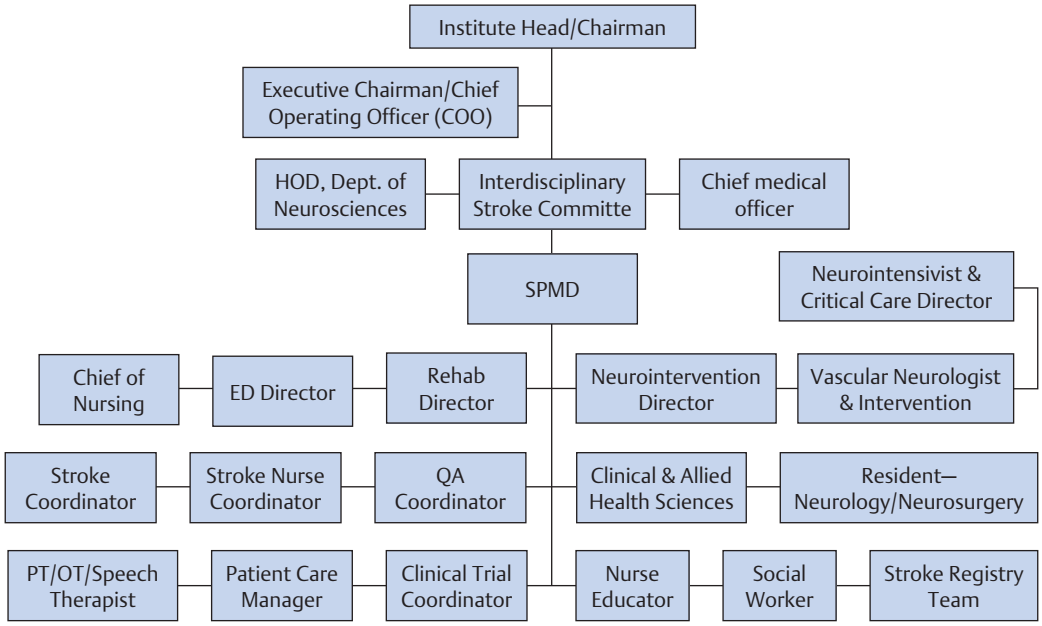

Fig. 29.1 Stroke program leadership.

Other Personnel Resources

A stroke team consisting of clinical and vascular neurologists, neurointerventionists, emergency physicians, neuroradiologists, neurosurgeons, neurocritical care physicians, stroke nurses, clinical pharmacists, research assistants, nurse manager, stroke coordinator, technical staff like CT/MRI technicians, neurointervention-trained Cathlab technicians and nurses, stroke data managers and analysts, rehab therapists (physical, occupational, and speech), patient care managers, social workers, and other supportive staff should be available 24/7.

Neuroimaging Capabilities

Neuroimaging capabilities include noncontrast CT, angio-CT, CT perfusion 24/7, MRI, MR angiogram, MR perfusion, carotid Doppler, and AI-assisted neuroimaging preferably transesophageal echocardiography (TEE) and transcranial Doppler (TCD).

Procedural Capabilities

Assessment and implementation of stroke care bundles for all admitted patients with a multidisciplinary team, including dysphagia screening, nutritional assessment, deep vein thrombosis (DVT) prophylaxis, antithrombotics, etc. in patients eligible to administer IV thrombolysis, mechanical thrombectomy, hemorrhagic stroke emergency management, advanced endovascular and neurosurgical management of subarachnoid hemorrhage (SAH) and other vascular lesions, intracranial hemorrhage (ICH) evacuation, ventriculostomy and emergency decompressive craniectomy, carotid revascularization, and carotid endarterectomy. There should be facilities and protocols for stroke mechanism workup to prevent and manage post-stroke complications with discharge checklist for secondary prevention, stroke education, and follow-up counseling. CSC should also have the capability of offering neurocritical care services for serious

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stroke patients requiring multidisciplinary management.

Hospital Bed Resources

Hospital bed resources include dedicated stroke unit, neurocritical care unit, stepdown and rehab ward, transfer center, and transport teams—mobile stroke unit, aeromedical or ground transport.

Quality Improvement and Clinical Research

Regular audits of performance measures, gap analysis, and action plans for correction. The conduct of ethics-approved research is an important CSC function. Professional publications and presentations are also encouraged.

Policies, Processes, and Protocols

The stroke center should establish written down policies and standard operating procedures for diagnosis, management, nursing, acute therapies, interventional therapies, neurosurgical options, rehabilitation, prevention, follow-up etc., which are to be revised and updated regularly.

Based on latest evidence, the center should design clinical practice guidelines on various aspects:

- Emergency management of acute ischemic stroke (AIS).
- Inpatient treatment of stroke.
- Management of hemorrhagic stroke.
- Transient ischemic attack with observational services.
- Management of aneurysmal SAH.
- Endovascular guidelines.

It is preferable to have written down policies for stroke care pathways in regards to the emergency medical services (EMS), prehospital stroke care, stroke ambulance, and emergency room (ER) triaging.

The creation of order set and treatments/management protocols provides a standardized approach to the care and treatment of stroke patients. This standardization allows for reduction of variation in the provision of clinical stroke care to patients and improves documentation, while allowing for incorporation of current, scientifically based clinical knowledge. There should be procedures and scales to be used for physical therapy, occupational therapy, and speech therapy.

Education and Research

Community education, community prevention, professional education, and patient education.

Network of Stroke Centers

There are two essential ways that a patient with stroke can get best possible outcomes. They have to go to the right place (stroke center) at the right time (within treatment window). The best outcomes result from evidence-based and earliest interventions. Acute stroke strikes as an emergency and the tendency is to go to the nearest medical facility. Given the time dependency of stroke treatments we have to identify and strengthen the links in the chain of survival, so that every stroke patient can access needed treatments within the golden hours.

Stroke Public Education

The crux is to identify stroke symptoms by the attenders/bystanders, which is possible by a regular and extensive public education programs about the basics of brain stroke to recognize the symptoms and the need to act immediately to call EMS/emergency transport to reach a stroke center as early as possible. Ideally all the eligible patients with AIS should receive IV thrombolysis as early as possible, at the latest 60 minutes after arrival. In case treating neurologists identify and/or the imaging shows large vessel occlusion

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the patient should be offered mechanical thrombectomy if available at the same center or transferred to the nearest CSC.

For this to happen we need to build a local stroke network with the CSC in the middle that is connected to about 5 to 10 regional PSCs which in turn serve community hospitals in that area.

Emergency Medical Services

The EMS system should be geared up to prioritize stroke as a medical emergency and to reach the nearest stroke center as early as possible with code stroke protocols for rapid evaluation and management.

Code Stroke Protocol in CSC

This is given in **Fig. 29.2.**

Concept of Certifying Stroke Centers

In the US the certification began in 2003. There are now four tiers starting with ASRH and progressing through thrombectomy capable and comprehensive centers.[11]

They recognized four levels of stroke centers now.

Need and Benefits of Certifications for Stroke Centers

An organized stroke care system is required for prompt recognition, response, and medical intervention which will translate into better outcomes. Stroke quality metrics play an important role in the quality improvement, patient outcomes, and enhanced patient safety.[12] Stroke center certification recognizes that a center has dedicated stroke-focused program with infrastructure and staffed by stroke team to meet the community stroke patients' needs. Certified stroke centers will increase the quality of stroke care and can provide improved efficiencies, reduce mortality rates, decrease length of hospital stay, improve long-term outcomes, and increase patient satisfaction.

Certification provides standardized and consistent stroke care across all the centers. The mandatory audits and calculation of performance measures on regular basis will create an environment of continuous quality improvement.

Stroke Center Certification in India

Resources in India: India is vast country with high stroke burden and the resources for optimal stroke care are limited and disproportionately distributed mostly in the urban centers. According to a recent survey, there are about 2,500 neurologists, 400 stroke units, 595 IVT capable centers, and 365 EVT capable centers.[13]

In India stroke center certification program was started by the Quality & Accreditation Institute (QAI) in collaboration with Indian Stroke Association. Ankineedu Stroke Center of Lalitha Superspecialities Hospital received the first certification as Advanced Stroke Center in June 2023. So far 17 centers have been certified as Advanced Stroke Centers and 1 as PSC in India. Another accreditation body was started by the National Accreditation Board for Hospitals and Healthcare Providers (NABH) in association with the WSO and so far three centers have been certified as CSCs.

- **Step A: Requirements and quality metrics:** Information can be obtained from the national accreditation bodies like the QAI,[14] NABH,[15] or international resources like the JCI, ESO, and WSO recommendations.

Checklist: To evaluate the initial assessment of the existing infrastructure and resources. Available acute stroke team personnel and expertise—neurologists, ED physician,

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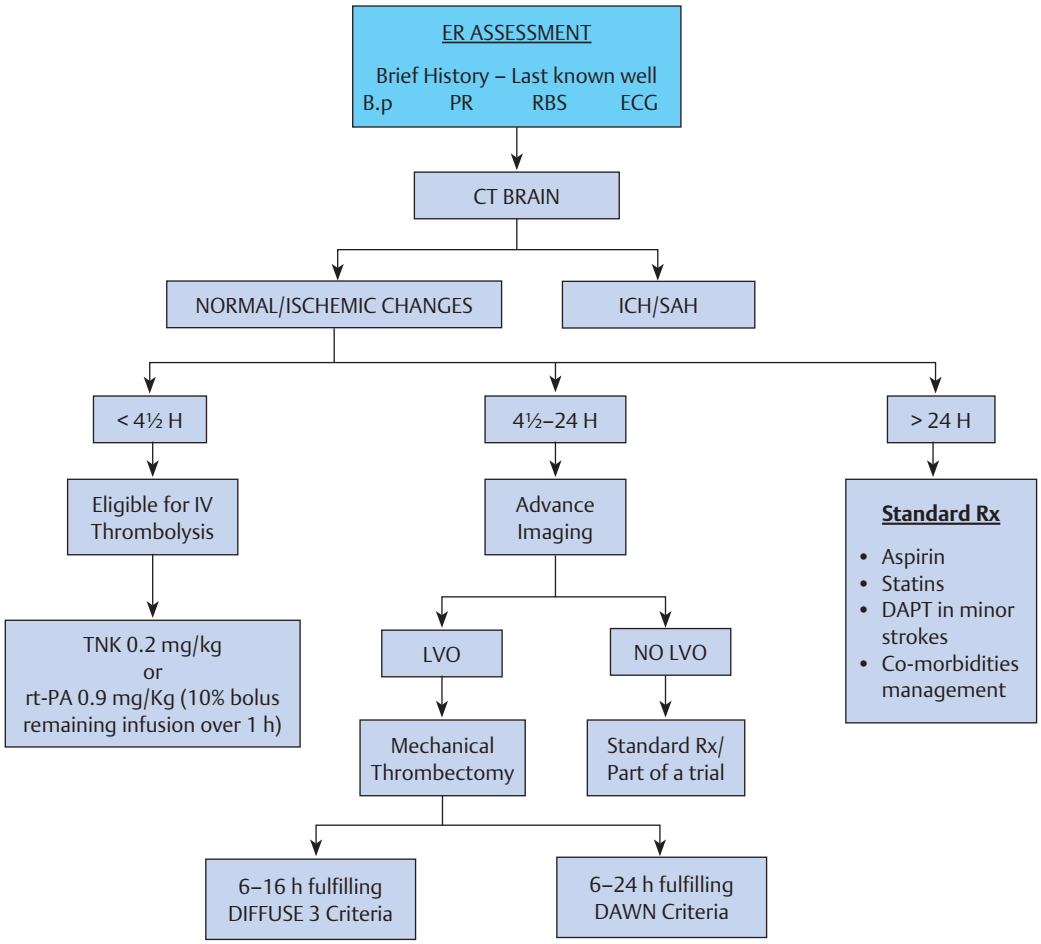

Symptom onset Date & Time	ER Time	CT Done Time	Door to needle Time (IVT)	Door to Puncture time for EVT	Door to Reperfusion time for EVT

Fig. 29.2 Code stroke protocol.

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neurosurgeons, neurointerventionists, nursing and paramedical team.

- **Step B: Checking the structural and process components:** To examine the existing infrastructure for available personnel and processes in the current stroke care pathway in your center.
- **Step C: Conduct of gap analysis:** To identify the deficiencies and constitute a task force to make an action plan and monitor implementation. It will take a few PDSA (Plan Do Study Act) cycles to arrange for all the necessary components. To develop stroke continuing medical education (CME) for staff training and physician training.
- **Step D: Action plan and implementation:** To check the self-assessment tool, we can use PDSA four-stage problem-solving model used for improving process or carrying out change. It may take several PDSA cycles and mock drills to optimize all the components of CSC.
- **Step E:** Apply for accreditation after meeting the criteria.
- **Step F:** After getting accreditation to maintain the same standards with regular internal audits and updates as required.

Challenges and Lessons Learned

- The CSC program requires commitment and investment from the institute for the advanced neurosurgery, neurointerventional radiology, neurocritical care, hospitalist services, and psychiatry. CSC leadership teams should include stakeholders from each of these services in addition to hospital administration, nursing, and ancillary department leadership. All stakeholders should have input in the gap analysis and action plans.
- Stroke science is dynamic and rapidly evolving and the presence and pivotal role of stroke program medical director should be emphasized.
- The number of neurointerventionists needed in our country is about 1000, but only about 200 trained neurointerventionists are available.
- Common pitfall: Even successful and busy PSCs that have provided care to stroke patients require restructuring and resource investment to develop a sustainable CSC program.
- There should be proper coordination and effective transfer protocols between PSCs and CSC.
- Field triage—logistics in drip and ship, integration and communication between EMS and the triage mechanisms for identifying eligible large vessel occlusion (LVO) strokes requiring mechanical thrombectomy.
- A CSC should be capable of managing two EVT patients simultaneously (which presumes 24/7 availability of stroke team and Cath team × 2).
- The present challenge is integration of CSCs into networks involving PSCs, ASRH, and community hospitals.
- **Continuous quality improvement is mandatory:** It is again interprofessional effort through which lessons are learned and new care protocols developed based on the performance gap identified.

Conclusion

CSCs have been shown to significantly affect outcomes of patients with complex and severe strokes. The addition of certification based on core set of standards would reduce variability in hospital workforce and resources that would further improve and strengthen stroke center services.[11] However, it is a cost and labor-intensive process which requires commitment and dedication by all stakeholders involved.

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References

1. Jones SP, Baqai K, Clegg A, et al. Stroke in India: a systematic review of the incidence, prevalence, and case fatality. Int J Stroke 2022;17(2):132–140
2. Lindsay P, Furie KL, Davis SM, Donnan GA, Norrving B. World Stroke Organization global stroke services guidelines and action plan. Int J Stroke 2014;9(Suppl A100):4–13
3. Stroke Unit Trialists' Collaboration. Organized inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002;(2):CD000197
4. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2013;2013(9):CD000197
5. Langhorne P, Ramachandra S; Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. Cochrane Database Syst Rev 2020;4(4):CD000197
6. Langhorne P, de Villiers L, Pandian JD. Applicability of stroke-unit care to low-income and middle-income countries. Lancet Neurol 2012;11(4):341–348
7. Adeoye O, Nyström KV, Yavagal DR, et al. Recommendations for the establishment of stroke systems of care: a 2019 update: a policy statement from the American Stroke Association. Stroke 2019;50(7):e187–e210
8. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA 2000;283(23):3102–3109
9. Alberts MJ, Latchaw RE, Selman WR, et al; Brain Attack Coalition. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. Stroke 2005;36(7):1597–1616
10. Meretoja A, Roine RO, Kaste M, et al. Effectiveness of primary and comprehensive stroke centers: PERFECT stroke: a nationwide observational study from Finland. Stroke 2010;41(6):1102–1107
11. Dusenbury W, Mathiesen C, Whaley M, et al; American Heart Association Council on Cardiovascular and Stroke Nursing and the Stroke Council. Ideal foundational requirements for stroke program development and growth: a scientific statement from the American Heart Association. Stroke 2023;54(4):e175–e187
12. Parker C, Schwamm LH, Fonarow GC, Smith EE, Reeves MJ. Stroke quality metrics: systematic reviews of the relationships to patient-centered outcomes and impact of public reporting. Stroke 2012;43(1):155–162
13. Sebastian IA, Gandhi DBC, Sylaja PN, et al. Stroke systems of care in South-East Asia Region (SEAR): commonalities and diversities. Lancet Reg Health Southeast Asia 2023;17:100289
14. Information Brochure for Accreditation of Primary Stroke Center and Advanced Stroke Center. QAI CAHSC 1601. Issue No. 03 | Issue Date: March 2024
15. National Accreditation Board for Hospitals and Healthcare Providers (NABH): Certification Standards for Stroke Center. 1st ed. September 2023

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30 Surgical Evaluation of Refractory Epilepsy: Can We Make a Cost-Effective Standardized Protocol for India?

Swapan Gupta

Introduction

Epilepsy impacts over 45 million globally with an annual incidence of 2.8 million.[1] Despite availability of more than 30 anti-seizure medications (ASMs) currently, almost 30 to 40% of epilepsy cases remain refractory despite optimal treatment with ASMs known as drug resistant or refractory epilepsy (DRE).[2] Surgery is a valuable option in up to 50% of such cases and has shown to be significantly superior to medical management in both adults[3] and pediatric population.[4] Surgery done specifically for the purpose of control of seizures is known as epilepsy surgery. The goal of epilepsy surgery is to render freedom from seizure and at the same time avoid neurological deficits. Epilepsy surgery is different from routine neurosurgeries in that it is done primarily for seizure management and hence a robust hypothesis regarding part of the brain that needs to be removed (known as the epileptogenic zone [EZ]) to achieve seizure freedom must be validated by thorough evaluation before the surgery called surgical, or more popularly presurgical, evaluation of drug-refractory epilepsy (PSE). The term presurgical is more apt as the evaluation is usually done by a neurologist trained in epilepsy. This is because resection of the obviously visible lesion may not always yield the desired outcome of seizure freedom. This is because of the following reasons. First, the neuroimaging lesion could be an incidentaloma. Second, the EZ may be more extensive than imaging lesion. Third, there could be multiple lesions or lesions near eloquent cortex. And last but not the least, the standard structural neuroimaging like magnetic resonance imaging (MRI) could be negative yet drug-resistant epilepsy could be amenable to surgical treatment. All these factors necessitate presurgical evaluation before epilepsy surgery.

Presurgical Evaluation of Drug-Resistant Epilepsy

Concept of Epileptogenic Zone

The core of presurgical evaluation revolves around delineation of the EZ. The EZ is defined as the minimum amount of cortex whose resection is necessary and sufficient to eliminate seizures. The term epileptogenic zone was first used by Jean Bancaud and Jean Talairach to indicate the "primary seizure organization," reflecting the fact that seizure activity was typically observed near-simultaneously in a set of connected structures rather than a single structure.[5]

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Later, Hans Luders gave the updated concept of EZ as we understand today.[6] This zone cannot be directly defined by any single test but is estimated through identification of several other zones through a battery of investigations (**Fig. 30.1**). However, all cases do not require all the tests, and each case merits its own particular set of investigatory tools. The challenge is to use the minimum tools and discern accurate EZ. As we go higher up the ladder of presurgical evaluation, the tests become costlier, technically demanding, and requiring sophisticated instruments. This is the reason the standard protocols for doing presurgical work are invariably necessary.

Establish Anti-Seizure Drug Resistance

Epilepsy surgery is currently only indicated for drug-resistant seizures although the trend is moving toward early surgery even before true drug resistance is documented, as absence of drug resistance is increasingly considered a predictor of better postsurgical outcome.[7] Nevertheless, the foremost step in presurgical evaluation is still documentation of drug-refractoriness. DRE is defined as "the failure of adequate trials of two tolerated and appropriately chosen and used ASM to achieve sustained seizure freedom for a sufficiently long period."[8] Current definition of DRE limits to two ASMs as addition of third ASM or more is not shown to be much beneficial.[9] A sufficiently long period is operationally defined for an individual patient as three times the most extended inter-seizure interval for that patient, or 1 year, whichever is longer. Before the diagnosis of DRE is made, the clinician must rule out pseudo-refractoriness. Between 20 and 40% of patients referred to epilepsy monitoring units (EMUs) for difficult-to-control seizures are ultimately found to have psychogenic non-epileptic seizures (PNES),[10] thus highlighting the importance of ruling out pseudo-resistance to avoid wastage of time and cost on presurgical evaluation. Following are the most common possible reasons of pseudo drug resistance:

- **Wrong diagnosis:** The doctor must rule out non-epileptic events. This is quickly done by taking a good history of the semiology of the event, circumstantial evidence, and associated psychiatric comorbidities. Usually, PNES are associated with long duration,

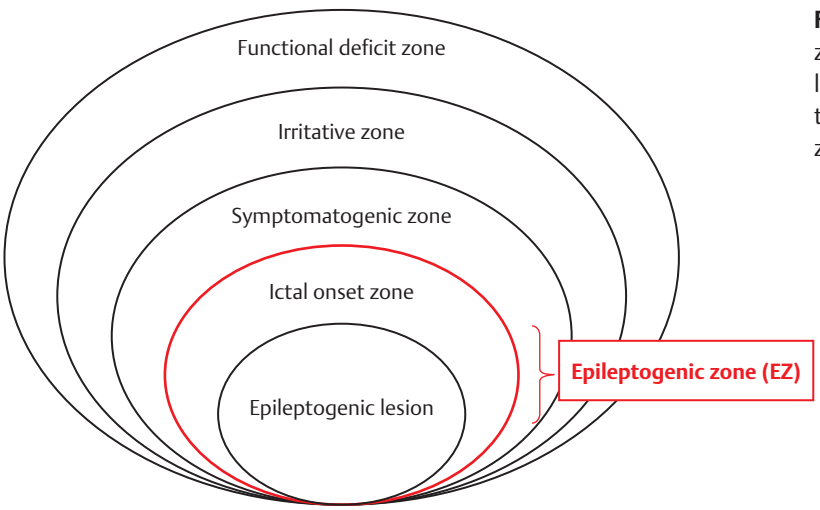

Fig. 30.1 The various zones to delineate epileptogenic zone. See text. EZ, epileptogenic zone.

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fluctuating course, asynchronous movements, pelvic thrusting, side-to-side head or body movements, closed eyes, ictal cry, and memory recall. On the other hand, occurrence in EEG-confirmed sleep, with post-ictal confusion, and with stertorous breathing favor epileptic seizure. Gradual onset, nonstereotyped events, flailing or thrashing movements, opisthotonos "arc en cercle," tongue biting, and urinary incontinence are insufficient to make an absolute distinction. In doubtful cases, a home video recording of the episode and video-EEG of the habitual event is helpful. Sometimes a patient may have both epileptic seizures and PNES. In such cases, usually PNES should be first managed before surgical management of resistant epileptic seizures.

- **Wrong drug:** The choice of ASM is usually based on the type of seizure. One should check the appropriateness of given ASM to the type of epilepsy. For example, sodium channel blockers are usually inappropriate for myoclonic epilepsies.
- **Wrong dosage:** One should try the maximum tolerated dose before labelling a drug as ineffective. Underdosing may result in pseudo drug resistance.
- **Compliance issues:** Missed pills, delayed dose, and comorbid conditions (sleep, fasting, fever, stress) must be addressed before epilepsy is labelled drug-resistant.

Phase 1 Presurgical Evaluation

Once the diagnosis of true drug-resistant epilepsy is made, the Phase 1 PSE is undertaken that includes video scalp EEG, high-resolution MRI, and detailed neuropsychological assessment. This is necessary in almost all cases except in few conditions where a part of it may be omitted in low-cost or nonavailability settings. These are discussed in detail in subsequent sections.

Video-EEG Long-Term Monitoring

Video-EEG long-term monitoring is done in specialized EMUs where patients are hooked to continuous scalp EEG with a continuously monitoring camera to record seizure events. ASMs are usually tapered in a staggered manner to bring the habitual seizures early on. The protocol for tapering ASMs depends on the seizure frequency, the type of seizures, and the number and type of ASM.[11] Usually, patients without prior status epilepticus or frequent daily seizures can undergo taper of each ASM by 30 to 50% one by one. There is no fixed count of number of seizures to be recorded but usually a minimum of 2 seizures in cases of localized MRI lesion with clinical and EEG concordance to more than 5 to 6 seizures if there is discordance are recorded. The aim should be to capture all kinds of habitual seizures.

Ictal symptomatogenic zone: The seizures recorded are analyzed for semiology (the sequence of events during a seizure) that, by the virtue of existing knowledge of particular areas of brain producing specific seizure manifestations, helps to find out the area of brain involved in seizure initiation and propagation. This is known as the ictal symptomatogenic zone. If the EZ is in primary sensory or motor cortex, the initial seizure manifestations may be related to the function of that cortex; in that situation, the ictal symptomatogenic zone corresponds to the area of initiation. However, in many instances, the initiation is from a silent cortex, and the initial clinical manifestations reflect activation of distant non-silent areas along the path of seizure propagation. The ictal symptomatogenic zone may be more valuable for lateralization than exact localization because it is most likely that seizures will spread within the hemisphere of origin before spreading to the contralateral hemisphere. Robust knowledge of semiology-related localization along with

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meticulous history and clinical examination is an important initial step for EZ hypothesis and does not need sophisticated tools. With advent of stereo-EEG (SEEG), accurate descriptions of seizure manifestations correlating with brain localization are available. Lack of in-depth knowledge results in poor hypothesis generation and unnecessary investigations raising the cost.

Ictal onset/seizure onset zone: The EEG recorded during the seizure determines the ictal onset zone which is also known as the seizure onset zone or pacemaker zone. Usually, the ictal onset zone coincides with EZ but may be false in localizing or lateralizing if the detected ictal activity may have already undergone considerable spread from where the seizure actually originated.

Irritative zone: This is the zone that generates interictal epileptiform discharges. This zone may be contained solely within EZ but can spread beyond it. It can be bilateral in mesial or basal cortices involvement or spread outside the true lobar localization. It can show generalized discharges especially with mesial focal lesions. Sometimes magnetoencephalography (MEG) may be employed in ambiguous cases.

Structural Brain Imaging

MRI of brain is the investigation of choice. CT may be required in suspected calcific lesions. The MRI could be positive for the abnormality or it could be negative. The MRI lesion is also called lesional zone. Before an MRI is considered negative, it should be assessed by a neuroradiologist specializing in epilepsy and then reviewed by a second neuroradiologist. Sometimes retrospective analysis after other investigations might delineate the occult lesions (**Fig. 30.2**). Presence of lesion on MRI is one of the strongest predictors of surgical success and avoids further expensive tests to find the lesion. Hence, importance of optimal MRI evaluation cannot be overemphasized. Although 3 Tesla MRI is better, a good-quality 1.5-T MRI could still be employed in case of nonavailability. Below 1.5 T is not recommended, and 7 T is not recommended in current guidelines. HARNESS (HARmonised Neuroimaging of Epilepsy Structural Sequences) protocol, including three-dimensional T1, coronal T2/FLAIR sequences, and sensitive sequences for hemosiderin and calcifications, is recommended by the International League Against Epilepsy (ILAE) for adequate sampling and at the same time

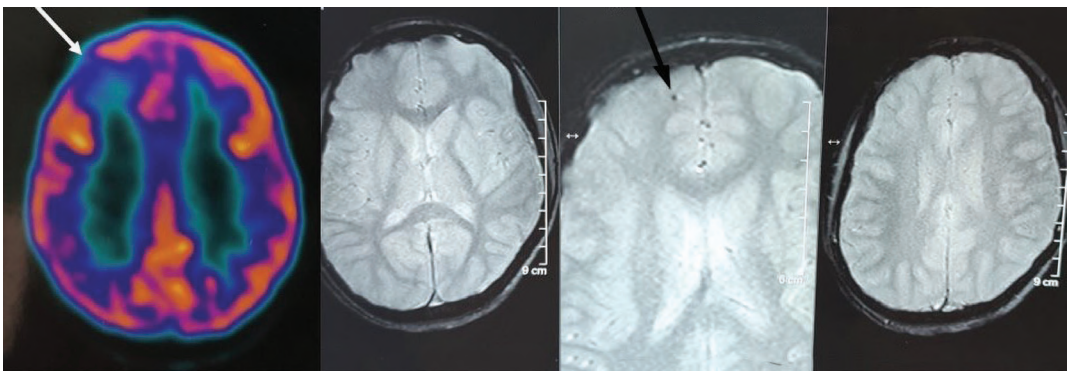

Fig. 30.2 Case of refractory epilepsy. A tiny calcification was seen adjacent to right anterior cingulate cortex in the gradient echo (GRE) sequence MRI of brain axial section (marked by black arrow) which was only detected after interictal positron emission tomography (PET) of brain revealed significant hypometabolism in right frontal region (marked by white arrow). The patient had daily seizures and after resection of calcific focus, the patient has been seizure-free for last 5 years.

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for saving on cost and time of acquisition.[12] Coronal T2 and FLAIR sequences should be angulated perpendicular to the hippocampal axis for hippocampal volume estimation. The relationship of the MRI lesion to the EZ is variable as discussed earlier. That is why surgery guided by "imaging-only approach" may not yield desired results.

Neuropsychological Testing

Neuropsychological testing helps in the determination of the functional deficit zone. The battery of tests evaluates cortical functions of left and right temporal, frontal, parietal, and occipital lobes. Some tests also help identify mesial versus lateral temporal dysfunction. Localizing information helps to support other tests in the presurgical evaluation. Neuropsychological testing helps to document preoperative deficits and can also help predict postoperative deficits, particularly when the planned resection will remove functioning cortex.

Phase 2 Presurgical Evaluation: Noninvasive

Once phase 1 presurgical investigations yield convincing evidence on localization of EZ, i.e., clinico-radiological–EEG concordance is achieved and sufficient information on the risk of potential postoperative deficits is obtained, the patient may be referred to surgery directly. If there are ambiguous results regarding EZ, further tests are performed under phase 2 presurgical evaluation. It is at this stage, the protocols become variable across the centers. This is largely influenced by the availability and cost of the tests as well as the experience of the investigator.

Functional Brain Imaging

The functional deficit zone is measured by positron emission tomography (PET) or single-photon emission computed tomography (SPECT). Hypometabolism on 18F-FDG–PET scan indicates a dysfunctional cortex, which can be related to the epileptic focus especially in temporal lobe epilepsies. It can be used to find occult lesion on MRI or as a surrogate marker in MRI-negative epilepsy (**Fig. 30.3**). PET-MRI co-registration increase the diagnostic yield for detecting potential epileptic lesions. PET hypometabolism that extends beyond the diseased temporal lobe or is remote from the epileptic source predicts a worse postsurgical outcome. Arterial spin labeling (ASL), also called as poor man's PET, obtained as part of structural MRI acquisition reveals focal hypoperfusion and can be used as a surrogate for PET. It can be used in resource-limited settings as a low-cost measure although more evidence regarding its definitive role in this regard is needed. 99mTc-hexamethyl propylene amine oxime (99mTc-HMPAO) SPECT, especially subtraction ictal SPECT, co-registered to MRI (SISCOM) showing localized areas of hyperperfusion is especially useful in nonlesional and extratemporal epilepsies. Ictal SPECT hyperperfusion occurs in both the ictal onset zone and regions connected to this zone, meaning that SPECT findings need to be considered in light of EEG, MRI, and PET results rather than serving as a single measure for the epileptogenic area.

Further tests under phase 2 presurgical evaluation depends on the requirement of the case and availability of the infrastructure. Hence, a set protocol as to in which order these should be done has to be individualized on case-to-case basis. These are high-end tools with cost and availability issues. A brief description about these tests and their usefulness is presented.

Magnetoencephalography (MEG)

MEG samples the magnetic correlate of electrical brain activity and, in contrast to EEG, is not attenuated by the conductance of the skull. MEG currently requires sensor cooling, which incurs high costs and limits the flexibility of the recordings. Source

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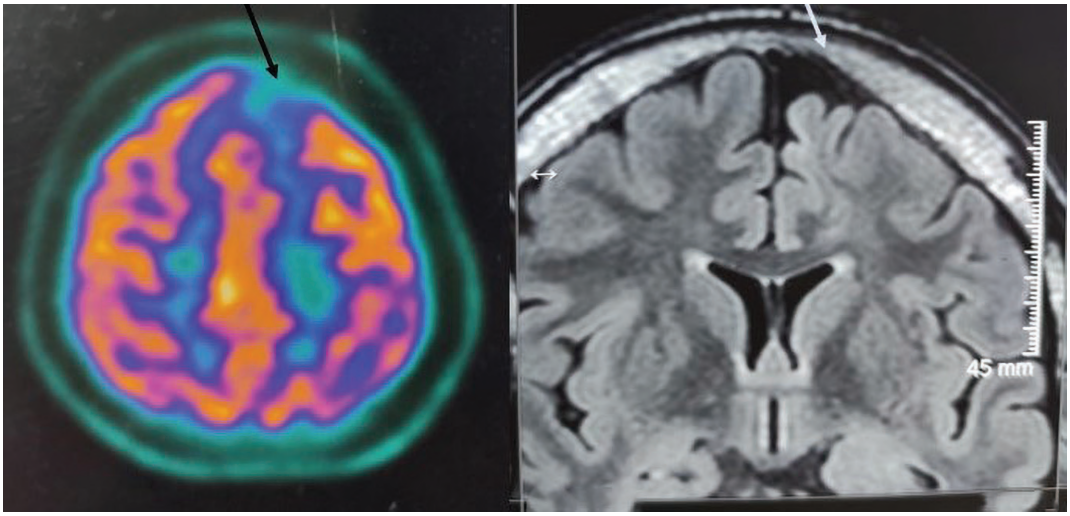

Fig. 30.3 Case of refractory epilepsy. The subtle cortical atrophy of left anterior cingulate seen on FLAIR sequence MRI coronal section (marked by white arrow), which was initially missed, was detected after interictal positron emission tomography (PET) showed significant hypometabolism in left mesial frontal region (marked by black arrow). Resection was done and the patient is seizure-free for 5 years. Biopsy showed type 1 focal cortical dysplasia.

estimation of interictal MEG is better than video-EEG at identifying the epileptogenic tissue (especially with tangential dipoles like in Rolandic epilepsies). Studies show that removing tissue with tight MEG spike clusters, especially if concordant with invasive EEG results, is associated with good postsurgical outcomes. MEG and EEG yield complementary information as interictal discharges (IEDs) are sometimes not adequately seen with only one modality.

Electrical Source Imaging

Estimation of the source of interictal epileptiform EEG discharges by high-density EEG (>30 electrodes) gives higher precision (HD-ESI). A combination of HD-ESI and MRI is shown to have good predictive value for seizure freedom after surgery. In the same manner, magnetic source imaging (MEG plus structural MRI) can be employed but limited availability and expertise prohibits its wide usability.

Combined EEG and Functional MRI

Interictal EEG–fMRI analyzes the changes on fMRI at the time IEDs occur on EEG. The spots of IED-related enhanced blood flow can direct planning of the depth of electrode placement during invasive evaluation, and removal of the spots with the most significant fMRI activation has been associated with good postsurgical outcomes. Availability is a major limiting factor in low-resource setting.

High-Resolution Structural Imaging

7-T MRI increases the signal-to-noise ratio for better detection of lesions. Abnormalities on 7-T MRI were found to be concordant with histopathological abnormalities. MRI postprocessing using hippocampal volumetry helps to lateralize temporal epilepsy. Voxel-based postprocessing of T1-weighted MRI scans using a morphometric analysis program (MAP) compares individual patient data with a database of regular scans. The abnormality on MAP can aid in the detection of the epileptogenic lesion.

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Diffusion Tensor Imaging

It enables the quantification of white matter tracts. It can be used to classify the side of the epileptic focus in patients with mesial–temporal epilepsy with good sensitivity and specificity. It can also guide the surgeon about the surgical approach by looking at the direction of displacement of the fibers by the lesion to avoid injury to the tracts (**Fig. 30.4**).

Postoperative Risk Assessment

In addition to the above tests for detection of EZ, the risk of potential postoperative deficits can be assessed by complementary investigations. fMRI for lateralization and localization of language, motor, and sometimes memory functions. Wada test for the same purposes has largely been superseded by fMRI and tractography to assess the risk of damage to white matter tracts, especially Meyer's loop and pyramidal tract, to assess the risk of postoperative visual fields and motor deficits, respectively.

Phase 2 Presurgical Evaluation—Invasive Evaluation

If the EZ cannot be localized with sufficient certainty with these noninvasive techniques, if noninvasive techniques yield divergent results, and/or if the presumed EZ is located in close proximity to functionally important brain areas and the patient is still considered a reasonable surgical candidate, intracranial EEG (IEEG) can be applied during a so-called phase 2 invasive evaluation. Chronic extraoperative IEEG techniques include the following:

Extraoperative IEEG through open craniotomy (CEEG): After open craniotomy, subdural grids or strips or a combination of depth electrodes and subdural electrodes are placed under direct observation.

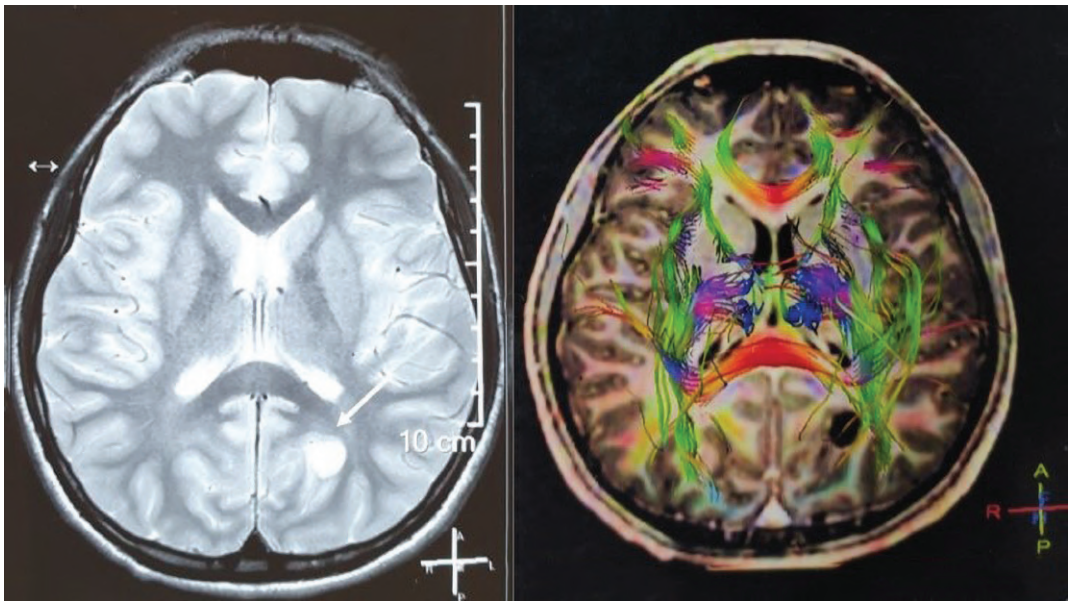

Fig. 30.4 A small cystic lesion (marked by white arrow) in the left occipital cortex seen in T2-weighted (T2W) MRI axial section causing refractory seizures. Vision and visual fields were normal. Diffusion tensor imaging (DTI) showed displaced visual white matter tracts laterally. It helped the surgeon plan a medial approach to avoid injury to visual fibers on the left.

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SEEG using intracerebral depth electrodes: Usually 5 to 18 multicontact electrodes are inserted through a twist drill hole or burr hole under general anesthesia. The electrodes are placed stereotactically with a frame, under neuronavigational guidance or with robotic assistance. The trajectories of the electrodes have to be planned thoroughly to avoid crossing blood vessels. In many centers there has been a shift from CEEG to SEEG, which is less invasive and much more comfortable for patients.

Intraoperative electrocorticography (ECoG): IEEG recordings and electrical stimulation mapping (ESM) are performed intraoperatively prior to, during, and often following resection using subdural, depth, or wick electrodes placed under direct visualization or guided by neuronavigation, representing an additional option, especially in patients with cortical dysplasia, tuberous sclerosis, or scalp EEG with continuous epileptiform discharges (CEDs), when extraoperative intracranial EEG is not feasible, and finally when surgery is performed adjacent to language or motor cortex. In some centers, it is routinely performed.

Levels of Epilepsy Centers

Based on the type of PSE, the centers for epilepsy surgery can be classified into those doing phase 1 and phase 2 PSE. Centers performing phase 2 PSE are big, large-volume centers equipped to do advanced presurgical workups.

Formulation of a Cost-Effective Standardized Protocol in a Resource-Limited Setting

Apart from the standard presurgical evaluation protocol for epilepsy surgery discussed above, additional factors that can help in customizing a low-cost standardized PSE protocol in a resource-limited setting are discussed in the following.

Avoidance of Unnecessary Evaluations

Not all patients are amenable to surgical therapy. Such patients are best managed with best medical therapy, avoiding unnecessary presurgical evaluations. It can avoid time-consuming, laborious, and costly tests. A screening tool to select the most appropriate candidate would be ideal, although there is none validated for clinical application currently. Following are the most common surgical indications as to when to consider surgical treatment:

- Adult candidates for epilepsy surgery:
  - Temporal epilepsies: Hippocampal sclerosis.
  - Cortical dysplasia.
  - Tumors.
  - Cavernoma.
  - Arteriovenous malformation (AVM).
- Pediatrics:
  - Extratemporal epilepsies: Cortical dysplasia.
  - Hemispheric epilepsies: Hemimegalencephaly, Rasmussen's encephalitis, congenital infarction, Sturge-Weber syndrome.

It is also important to know the contraindications. The relative contraindications for epilepsy surgery are:

- Progressive medical or neurological disorder.
- Primary generalized epilepsy.
- Minor seizures which do not impair the quality of life.
- Active psychosis that is not related to peri-ictal period.
- Poor contralateral memory function (for temporal lobectomy).

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Knowledge of Common Surgical Substrates and Their Standard Management

Considerable data are now available to guide on how far to evaluate a specific epilepsy case before resorting to surgery. Surgical management of drug-resistant epilepsies is an evolving field and hence the protocols are subject to change with advancements in both knowledge and technology. Although each case merits its own set of investigations but as a general guide, following could be adapted:

- Patients who can be selected by noninvasive studies (phase 1 only): This is when there is concordant data of various zones, viz., symptomatogenic zone, irritative zone, ictal onset zone, functional deficit zone, and lesional zone, so that there is a single, well-identified EZ. Phase 1 PSE, i.e., long-term Video-EEG (VEEG) monitoring, high-resolution structural MRI, and neuropsychological assessment, is usually sufficient. Following are the cases which usually follow this pattern:
  - Mesial temporal lobe epilepsy associated with hippocampal sclerosis.
  - Circumscribed epileptogenic lesions (not near eloquent areas):
    - Benign neoplasms.
    - Gangliogliomas.
    - Dysembryoblastic neuroepithelial tumors.
    - Low-grade astrocytoma.
    - Oligodendroglioma.
    - Vascular malformations.
    - Atrophic scars.
  - Large unihemispheric epileptogenic lesions (for hemispherotomy):
    - Hemiconvulsion hemiplegia epilepsy syndrome (HHE).
    - Sturge-Weber syndrome.
    - Rasmussen's encephalitis.
    - Hemimegalencephaly.
  - Epileptic encephalopathies and multifocal disease (for corpus callosotomy):
    - Lennox-Gastaut syndrome.

Cases of mesial temporal lobe epilepsy with a single discrete structural lesion need special mention. These constitute a major proportion of patients undergoing epilepsy surgery in most series. The surgical substrate includes mesial temporal sclerosis (MTS) or a single benign tumor (dysembyroblastic neuroectodermal tumor [DNET] ganglioglioma, low-grade glioma) or cavernoma. It has been shown in various studies that even in the absence of formal VEEG long-term evaluation, standard interictal EEG or ictal EEG with/without video have similar results of surgical outcome as with VEEG long-term evaluations.[17] This is especially important in resource-limited settings where VEEG facilities may not be available. However, a trained neurologist must be available to interpret the EEG data to prove concordance.

- Patients who require functional imaging/mapping and/or invasive studies:
  - Temporal lobe epilepsy with
    - Discordant electroclinical data.
    - Bilateral mesial temporal sclerosis.
  - Normal MRI.
  - Extratemporal circumscribed epileptogenic
    - Lesions close to eloquent area.
    - Malformations of cortical development.
  - Dual pathologies.
- Additional evaluation (only in select cases): It includes functional studies (interictal and ictal SPECT and/or PET) and/or MEG in cases where:
  - Results are discordant or nonlocalizing.
  - Guidance is required for placement of intracranial electrodes.

Invasive evaluation is indicated if and only if a hypothesis of a single, spatially constrained,

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potentially operable region is supported by noninvasive data. There is a 5 SENSE score which is a screening tool to guide about implantation.[18] The positive predictive variables are:

- Presence of focal lesion on MRI.
- Absence of bilateral independent spikes in scalp EEG (with the exception of bitemporal spikes).
- Localizing neuropsychological deficits.
- Strongly localizing semiology.
- Regional ictal scalp EEG onset.

National Epilepsy Surgery Program Framework

To conclude, a framework model of national epilepsy surgery program to deal with the large surgical treatment gap should be in place. In India with over 1.4 billion people, around 1 million people have medically refractory epilepsies. Nearly one half are potential surgical candidates. Only <5000 people with epilepsy have undergone epilepsy surgery till date. Even in the US, <1% of patients with continuing seizures are referred to epilepsy centers with the delay from onset of epilepsy averaging >20 years, resulting in impaired social and educational development. In a spoke and hub model few large-volume regional centers can act as hub and other centers in the vicinity as spokes for that regional center. Phase 1 evaluations with minimum requirements can be done at all centers while regional centers should be equipped for more sophisticated and advanced phase 2 evaluations. It will allow a greater number of surgeries to be performed with nodal centers well equipped for difficult cases that need phase 2 evaluations.

Summary

Here is a step-by-step summary to the approach of presurgical evaluation of refractory epilepsy:

Step 1: Recognition of seizure type and epilepsy syndrome.

Step 2: Adequate and appropriate trial of ASMs—define DRE.

Step 3: Possibility of surgical management of epilepsy to be explored.

Step 4: Start with minimum noninvasive presurgical assessments (phase 1).

Step 5: If clear hypothesis of EZ, strictly concordant data—perform surgery.

Step 6: If clear hypothesis of EZ, some doubt of concordance—perform additional noninvasive tests; in case of concordance—surgery.

Step 7: If hypothesis of EZ is present, but discordant data or EZ close to eloquent areas—explore preimplantation protocol (invasive).

Step 8: No hypothesis or multiple hypothesis or step 6 does not yield clear seizure-onset zone—best medical treatment/palliative procedures.

References

1. GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Apr;18(4):357–375.
2. Sultana B, Panzini MA, Veilleux Carpentier A, et al. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. Neurology 2021;96(17):805–817
3. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345(5):311–318
4. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for drug-resistant epilepsy in children. N Engl J Med 2017;377(17):1639–1647
5. Bancaud J, Talairach J, Bonis A. La stéréo-électroencéphalographie dans l'épilepsie: informations neurophysiopathologiques apportées par l'investigation fonctionnelle stéréotaxique. Paris: Masson; 1965

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6. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. Brain. 2001; 124: 1683–1700
7. Pelliccia V, Deleo F, Gozzo F, et al. Early epilepsy surgery for non drug-resistant patients. Epilepsy Behav Rep 2022;19:100542
8. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–1077
9. Mula M, Zaccara G, Galimberti CA, et al. Validated outcome of treatment changes according to International League Against Epilepsy criteria in adults with drug-resistant focal epilepsy. Epilepsia 2019;60(6):1114–1123
10. Anzellotti F, Dono F, Evangelista G, et al. Psychogenic non-epileptic seizures and pseudo-refractory epilepsy, a management challenge. Front Neurol 2020;11:461
11. Liu J, Chen D, Xu Y, Zhang Y, Liu L. Safety and efficacy of rapid withdrawal of anti-seizure medication during long-term video-EEG monitoring. Front Neurol 2023;14:1196078
12. Bernasconi A, Cendes F, Theodore WH, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia 2019;60(6):1054–1068
13. Carrette E, Stefan H. Evidence for the Role of Magnetic Source Imaging in the Presurgical Evaluation of Refractory Epilepsy Patients. Front Neurol. 2019 Sep 10;10:933
14. Murakami H, Wang ZI, Marashly A, et al. Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. Brain. 2016 Nov 1;139(11): 2935–2947
15. Choi JY, Wang ZI. Merging Magnetoencephalography into Epilepsy Presurgical Work-up Under the Framework of Multimodal Integration. Neuroimaging Clin N Am. 2020 May;30(2):249-259
16. Bear J, Kirsch H. Concordance between interictal MEG and stereo-EEG predicts seizure freedom after epilepsy surgery. Brain. 2016 Nov 1;139(11):2821-2823.
17. Castro-Villablanca F, Moeller F, Pujar S, et al. Seizure outcome determinants in children after surgery for single unilateral lesions on magnetic resonance imaging: role of preoperative ictal and interictal electroencephalography. Epilepsia 2022;63(12):3168–3179
18. Astner-Rohracher A, Zimmermann G, Avigdor T, et al. Development and validation of the 5-SENSE score to predict focality of the seizure-onset zone as assessed by stereoelectroencephalography. JAMA Neurol 2022;79(1):70–79

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31 Hearing and Facial Preservation in Acoustic Neuroma—Tips and Technical Nuances

Basant K. Misra, Abhijit Warade, and Alay Khandhar

Introduction and General Overview of Vestibular Schwannoma

The history and progress of vestibular schwannoma (VS) management parallels that of neurosurgery.[1] This chapter focuses on tips and nuances that have evolved in the management of VS over a considerable period. The present-day trend of minimal invasiveness has a major influence in the management of patients with VS.[1] VS is benign neoplasm that arises from the myelin sheath of the 8th cranial nerve at the transition zone between central and peripheral myelin.[2,3] They account for 8% of all intracranial tumors and 80% of cerebellopontine angle (CPA) tumors.[4] Treatment options include microsurgery, fractionated stereotactic radiotherapy, stereotactic radiosurgery, and a combination of surgery and radiotherapy or observation.[1,5] The average growth rate ranges from 2 to 4 mm per year in 50% of the cases, whereas less than 10% can regress.[6] The extracanalicular tumors are more likely to grow than those located within the internal auditory canal (IAC).[7] Tumor expansion in the CPA causes compression of the brain stem and leads to life-threatening neurological complications.

Clinical Manifestations

Incidental Tumors

Due to the wide availability of magnetic resonance imaging (MRI) currently and a decreased threshold for investigations, patients are often screened for minor trauma, nonspecific headache, or neurological symptoms and occasionally incidental VS is picked up.

Symptomatic Tumors

Unilateral hearing loss is the most common presenting symptom in 95% of patients. The other presenting symptoms include tinnitus and disequilibrium due to direct effects on the 8th cranial nerve and the inner ear structures.[8,9] The degree of hearing loss is not dependent on the size of tumor; thus, an intracanalicular VS can have profound ipsilateral deafness while a giant tumor can have useful serviceable hearing.[10] Classical presentation of high-frequency sensorineural hearing loss (SNHL) and a poor word recognition score out of proportion to the pure tone hearing loss is commonly seen. The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) committee on hearing and equilibrium recommends screening by imaging for a VS in

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any patient with >15 dB of pure tone loss at any one tested frequency or >10 dB hearing loss at two contiguous frequencies.[11] The next most common symptom is related to trigeminal neuropathy in 3% of cases.[8,12,13] Other unusual presentations include hemifacial spasms and giant tumors causing compression of the brain stem and fourth ventricle leading to corresponding symptoms like severe disequilibrium, nausea, vomiting, altered sensorium, and visual compromise.[14]

Vestibular Schwannoma Classifications

There are multiple classifications of VS proposed in the literature, depending on the size and extension of the tumor[15–18] (**Table 31.1**). The Koos classification and the Hannover classification are the most widely used.

Preoperative Evaluation and Grading of Hearing Loss

To choose the best course of action, it is important to identify the degree of hearing loss, and a crucial step in this therapeutic decision-making process is speech discrimination. Classification by AAO-HNS committee on hearing and equilibrium (**Table 31.2**) and the Gardner–Robertson classification system (**Table 31.3**) have been widely used for this purpose.[19,20] As per the AAO-HNS definition, serviceable hearing is defined by a pure-tone average of 50 dB or less and a speech discrimination score (SDS) of 50% or more (referred to as the 50/50 rule).[20]

Management Options

Treatment options include observation with serial neuroimaging, microsurgical resection, and radiosurgery. Age of the patient, comorbidity, tumor size, preoperative hearing status, and anatomy of the tumor influence the management strategy.[3] There are four classical steps in the surgical removal of a VS: (1) intracapsular tumor removal; (2) identification of facial and cochlear nerves at the IAC; (3) nerve identification and dissection medially next to the brain stem; and (4) complete removal of the tumor under direct vision of those structures. The goal is to obtain an

Table 31.1 Various classifications of vestibular schwannoma[15–18]

Maximum diameter of tumor (in mm)	Tumor description	Classification systems			
		Sterker[15]	House[16]	Koos[17]	Hannover[18]
0	Confined to IAC	Tube	Intracanalicular	Grade I	T1
≤10	Occupying IAC	Small	Grade 1 (small)	Grade II	T2
≤15	Occupying CPA		Grade 2 (medium)		T3a
≤20		Mild			
≤30	Occupying CPA and contacting the brain stem		Grade 3 (moderately large)	Grade III	T3b
≤40	Compressing the brain stem	Large	Grade 4 (large)	Grade IV	T4a
>40	Severe brain stem compression and fourth ventricle displacement by tumor	Huge	Grade 5 (Giant)		T4b

Abbreviations: CPA, cerebellopontine angle; IAC, internal auditory canal; mm, millimeter.

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Table 31.2 American Academy of Otolaryngology–Head and Neck Surgery hearing classification of hearing loss[19]

American Academy of Otolaryngology–Head and Neck Surgery Hearing Classification		
Class	**PTA (dB)**	**SDS (%)**
A: Good	≤30	≥70
B: Serviceable	>30 to ≤50	≥50
C: Capable of aid	>50	≥50
D: Nonfunctional	Any level	<50

Abbreviations: dB, decibel hearing loss; PTA, pure tone audiometry; SDS, speech discrimination score.

Table 31.3 Gardner–Robertson modified hearing classification of hearing loss[20]

Gardner–Robertson Modified Hearing Classification		
Class	**PTA (dB)**	**SDS (%)**
I: Good	0–30	70–100
II: Serviceable	31–50	50–69
III: Nonserviceable	51–90	5–49
IV: Poor	91–maximum	1–4
V: None	Not testable	0

Abbreviations: dB, decibel hearing loss; PTA, pure tone audiometry; SDS, speech discrimination score.

arachnoid veil at the CPA after the tumor removal, where the facial nerve (FN) is barely seen through it. The lesser the exposure of the FN the better is the functional result.[21]

Goals of Treatment

Functional preservation and a normal face are the primary goals for any approach and for all sizes of tumor. Hearing preservation is the primary aim in patients with small- to medium-sized tumors (smaller than 2.0 cm), primarily intracanalicular tumors, and in those with preoperative serviceable hearing (classes A and B).[3]

Microsurgical Approach

There are three common microsurgical surgical approaches to VS, namely, retrosigmoid craniotomy (RSSOC), middle fossa, and translabyrinthine approach; each one of them have their potential benefits and disadvantages[3,22,23] (**Table 31.4**).

RSSOC is the workhorse, posterior-to-anterior approach for all size of tumors, versatile and familiar to most neurosurgeons, and the preferred approach of the authors. All sizes of tumors can be operated by RSSOC. Since the bony anchoring of the tumor is at the internal auditory meatus (IAM) which can be reached after tumor decompression, the authors do not recommend the more extensive approach of translabyrinthine in VS.[1] Moreover, once cerebrospinal fluid (CSF) is released from the cerebello-medullary cistern, one of the first steps after dural opening, no or minimum cerebellar retraction is necessary. IAC can be drilled to achieve total tumor excision. Both good facial function and hearing preservation are possible. It allows early identification of the proximal FN along the brain stem and drilling of IAC allows distal identification of the nerves.[3]

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Table 31.4 Advantages and disadvantages of common surgical approaches for vestibular schwannoma[3,22,23]

	RSSOC	MCF	TL
Advantages	• Wide exposure of CPA • Feasible in all sizes of tumor • Good possibility of hearing preservation • Early identification of the facial nerve REZ and good possibility of facial preservation	• Good possibility of hearing preservation • Early exposure of the lateral IAC • Excellent exposure of intracanalicular tumor	• Early exposure of the lateral IAC and facial nerve • Drilling and bleeding during approach are extracranial • No retraction of temporal lobe or cerebellum
Disadvantages	• Need for cerebellar retraction • Need of intradural drilling to access IAC • Postoperative headaches	• Need for temporal lobe retraction • Limited exposure of brain stem • Unsuitable for large tumors	• Ipsilateral deafness • Increased operative time • Unfamiliar approach for neurosurgeons

Abbreviations: CPA, cerebellopontine angle; IAC, internal auditory canal; MCF, middle cranial fossa approach; RSSOC, retrosigmoid suboccipital craniotomy; REZ, root entry zone; TL, translabyrinthine approach.

Middle cranial fossa approach (MCF) is a superior-to-inferior approach, preferred for smaller intracanalicular tumors and for hearing-preservation surgery.[23] Surgical pearls mentioned by Budohoski et al in their publication mention IAC to be drilled to achieve a >180 degrees (ideally 270 degrees) canal opening over the region of the mass of the tumor to enable more room for mobilization of the tumor without transmitting pressure to the overlying FN and the underlying cochlear nerve.[24] The tumor has to be debulked prior to extratumoral dissection from these nerves and FN then gently mobilized from top of the tumor, usually anteriorly, and the cochlear nerve is respected during dissection, taking care not to injure it blindly with the hook dissector prior to tumor removal. Thus, the hearing preservation rates using this approach are higher with 78% of patients maintaining AAO-HNS class A or B hearing.[24]

Translabyrinthine (TL) is a lateral-to-medial approach to tumors. Hearing is sacrificed in this approach and is usually done in patients without serviceable hearing or large tumors wherein preservation rates are lower.[3]

It is known that the results of VS surgery depend more on the individual surgeon's experience than on the advantages or disadvantages of a particular approach.[25] However, the application of an extra cisternal technique may reduce the surgeon's learning curve and improve VS surgical results; thus, the results achieved were an overall gross-total resection (GTR) in 81% and good FN function in 93% of the patients.[18,26–29]

Facial Nerve Preservation—Tips and Nuances

Facial palsy is a major cause of unhappiness for the patient. Once the nerve is damaged, we, the tough surgeons, eventually forget but unfortunately, the patient will never forget; hence, all attempts should be made to preserve FN function. House and Brackmann (HB) devised a grading system to evaluate FN function which is used universally[30] (**Table 31.5**).

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Table 31.5 House–Brackmann facial weakness grading scale[30]

Score	Gross	At rest	At motion
I	Normal	Normal	Normal
II	Slight weakness noticeable on close inspection	Normal symmetry and tone	Forehead—moderate to good function Eye—complete closure with minimal efforts Mouth—slight asymmetry
III	Obvious but not disfiguring difference	Normal symmetry and tone	Forehead—slight to moderate movement Eye—complete closure with efforts Mouth—slightly weak with maximum efforts
IV	Obvious and/or disfiguring asymmetry	Normal symmetry and tone	Forehead—no movement Eye—incomplete closure Mouth—no movement
V	Barely perceptible motion	Asymmetry	Forehead—no movement Eye—incomplete closure Mouth—slight movement
VI	No movement	No movement	No movement

FN function is considered satisfactory as long as the HB grading is 3 or less. A systematic review of 89 articles on FN function reported a 78% rate of preservation with the RSSOC approach in tumor size <20 mm and 67% in larger tumors.[31] The change of trends in FN preservation over a period of time in the series by Misra et al is clear. FN preservation was high at 96% in 2008 as compared to 77% in 1993 owing to the trade-off between lower total excision rate (83% in 2008 compared to 94% in 1993) because of the recent emphasis on good facial function. This is achieved by leaving a thin sliver of tumor over the FN, which may or may not grow on subsequent follow-ups, and if they grow, they can be offered either radiosurgery or redo-surgery with excellent facial preservation results. They recommend microsurgery as the first choice in young patients with tumors less than 2.5 cm as their results in this group were excellent with 100% preservation of facial function and eradication of the tumor for good.[1] FN preservation rate in the study by Rajput et al, where all patients had large tumors, was 56% considering HB grade III or less as acceptable FN function.[2] Anatomically, the FN is quite resistant to tumor infiltration and dysfunction from the stretch occurring due to the slowly growing VS.[2] Axon and Ramsden stated that theoretically, HB grade I FN function can be maintained with only 10% of motor neurons functioning; however, the nerve is prone to damage secondary to intraoperative manipulation.[32]

Intraoperative neuromonitoring (IONM) is now the gold standard and a mandate during VS surgery for FN preservation for all sizes of tumors. It helps in early localization, minimization of trauma during dissection, and ensures functional integrity during surgery.[33] Monitoring ensures good long-term facial function with the HB grade usually improving 1 to 2 points in the next 3 to 6 months of the postoperative period.[34,35] Most centers use two-channel electromyography for intraoperative monitoring of the FN, commonly observing the function of the orbicularis oculi and the orbicularis oris muscles, although other muscles can also be used. At our center we do monitoring for the mentioned muscles as well as frontalis and mentalis.[36] Baseline readings are obtained once the final position of the patient is attained in the operating room but before making the skin incision. A direct stimulation probe is then applied to the

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suspected areas of FN course and an electrical stimulus delivered. Once the amplitude of the extrinsic stimulus exceeds the nerve's threshold for action potential, twitching of the facial muscles is observed and detected by the electrodes. Multiple waveforms of motor potentials have been described, and can be studied by the electrophysiologist in the operating room to provide additional feedback regarding the health of the nerve.[37] Additionally, at the conclusion of the operation, the threshold at which a response can be elicited is ascertained; lower thresholds have been shown to have a good prognostic value with regard to FN function.

Magnetic Resonance Imaging

Churi et al evaluated correlation between diffusion tensor imaging (DTI) and intraoperative findings for nerve location in relation to the tumor in the cistern. Study showed the correlations between the DTI and intraoperative findings for the facial, trigeminal, and vestibulocochlear nerves were 85% (34 of 40), 85% (34 of 40), and 75% (12 of 16), respectively. Thus, it highlighted the fact that this modified technical parameters proposed can lead to better preservation of cranial nerve function, especially for patients with large tumors.[38] Savardekar et al reported that preoperative DTI with fiber tracking for FN identification is a useful diagnostic tool before surgery for masses larger than 2.5 cm. FN course was identified in 96.6% cases in their study preoperatively; however, the intraoperative confirmation was in 90.6%.[39] Zhang et al reported that through fast imaging employing steady-state acquisition (FIESTA) study, it is possible to see the FN in the cisternal segment provided that there is a CSF signal between the nerve and the neoplasm.[40–42] Farid and Elkholy6in their study found that in 93.75% of the patients, location of the FN was anterior, anterosuperior, and anteroinferior to the capsule. Near-total resection was higher when the nerve was anteriorly located (P = 0.001) while subtotal resection was higher when the nerve was posteriorly located (P = 0.021). They concluded that subtotal resection was associated with a better facial preservation (HB grade I) at 83%.[42]

Anatomical considerations: FN located dorsal to the tumor or engulfment of the nerve by a lobulated tumor or in tumor capsule increases the risk of nerve injury.[43]

Tumor-related factors: Features such as vascular, adherent, fibrous, and engulfment of adjacent nerves and vessels (VAFE) make dissection of tumor from the FN or brain stem tedious and the risk of damage increases. This is commonly seen during the last 10 mm of tumor resection and the surgeon should be vigilant and use frequent nerve stimulation for the precise delineation of the FN to preserve function.[43] Ramina et al in their study mentioned patients with intracanalicular VS who underwent resection via retrosigmoid approach and tumors located between facial and vestibular nerves achieved worse hearing and facial outcomes than those with tumors located posterior to the vestibular nerves.[44]

Tumor recurrence: Redo surgery of post-radiation recurrence leads to increased adhesiveness of the tumor to the FN or the brain stem, hence putting the FN at an increased risk of injury.[5,45,46]

Risk of damage to the FN: There is risk of FN damage secondary to coagulation and manipulation of the nerve. There is also significant risk to the nerve from the heat of drilling IAC. Hence, it is important to continuously irrigate while drilling. It is imperative to identify the superior or inferior edge of the FN on the tumor capsule with IONM, prior to dissection, and careful dissection under the firing sound of NM helps limit damage to the FN.[3]

Near-total resection: GTR has the lowest recurrence rate and is the goal of microsurgery. There has been, however, now a paradigm shift to subtotal or near-total resection with more emphasis on preservation of function.

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Intraoperatively, if there is a high risk of damaging critical neurological structures, a near-total resection can be pursued which has nearly 13 times less chance of recurrence compared to subtotal resection.[47] This is where intraoperative FN and brainstem evoked response audiometry (BERA) monitoring makes a significant difference.

Surgeon's experience: Most researchers agree that facial function preservation is better when the tumor is smaller, the surgeon is experienced, and the tumor is approached using a technique that the surgeon is most familiar with.[3]

Hearing Preservation—Tips and Nuances

Brain stem auditory evoked response (BAER) is the neural activity elicited by stimulation of the 8th cranial nerve.[48] The averaged results of multiple stimulations, after the background noise has been subtracted, produce seven characteristic waves. For prognostication purposes, changes in waves I, III, and V are the most significant.[49] Intraoperatively decreased amplitudes and/or increased interpeak latencies should prompt caution on the part of the surgeon. When the waves are preserved, one can be reassured of a good outcome. However, once the waveforms deviate from the baseline, one cannot reliably predict the presence or degree of postoperative deficit.[37] One of the most important shortcomings of BAER IOM is the delay caused by the need to average the signal over multiple stimulations. As a result, a change in the waveforms may be the consequence of manipulation that occurred seconds to minutes prior to the alert.[49] Moreover, baseline BAER is commonly abnormal or absent in patients harboring large tumors that precludes its use as a surgical adjunct.

Direct Cochlear Nerve Action Potential (CNAP) Monitoring

The cochlear action potential is measured directly from the 8th cranial nerve. After placement of a negative electrode at the contralateral mastoid and a scalp reference electrode, a recording electrode is placed directly on the nerve proximal to the tumor resection and an external auditory stimulus is applied. The resulting action potential is measured, and typically results in two negative peaks with high amplitude designated "N1" and "N2."[49] Changes to the latency or amplitude of the N1 peak suggest neural injury. Compared to BAERs, direct CNAPs have the advantage of faster response times. However, the recording electrode is relatively bulky and because its use is limited to cases in which adequate exposure can be obtained, it is often impractical to use during the middle cranial fossa (MCF) approach.

Surgical Approaches and Size of Tumor

A good exposure and an early identification of vestibular nerve fibers is important for tumor debulking while preserving the cochlear nerve.[50] MCF and retrosigmoid approaches are options for hearing-preservation cases with the middle fossa approach being the best, subject to size of the tumor and exposure obtained.

Size of Tumor

Hearing preservation is usually attempted in tumors <2.5 cm.[50–58] Increased rates of hearing preservation in large tumors is seen due to better selection criteria and deciding for a near-total or a subtotal resection under BERA monitoring.[43]

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Preoperative Hearing Status

AAO-A/B is classified as >50% SDS and it is considered as useful hearing (**Table 31.3**). Hearing-preservation surgery is considered only for patients with >50% SDSs preoperatively.[50–58]

Anatomical Factors

Preservation of the anterior inferior cerebellar artery (AICA), encountered during the surgery, and the labyrinthine artery, the branch of AICA running along the 8th nerve, is essential to preserve hearing.[3]

Surgical Factors

Dense adhesions, nerve retraction, nerve ischemia, heat or mechanical damage of the nerve, and damage to labyrinth during IAC drilling can lead to hearing loss.[43]

Surgical Technique

If hearing is to be saved, then sharp dissection is required to separate the tumor from the fibers of the 8th nerve. Dissection should proceed from the brain stem to the IAC to avoid putting undue traction on the distal cochlear nerve fibers where they are most fragile.[3]

Reasons and Regions of 7th and 8th Cranial Nerve Injury

- Just medial to IAM:
  - Mechanical.
  - Maximum adherence.
  - Sharp angle between intracanalicular (IC) and extra-canalicular (EC) tumor.
- At the brain stem:
  - Venous injury.
- Inside IAM:
  - Arterial injury.
  - Thermal injury (coagulation/drilling).
    - Labyrinth injury: Avoid.
    - Endoscopic approach for removing the lateral part of the tumor in IAM.

General Operative Nuances in Vestibular Schwannoma Surgery

The principles of VS surgery for preservation of neural structures are bloodless microdissection, progressive debulking, minimal use of the retractors and bipolar coagulation, meticulous manipulation of the flattened nerves, capsular elevation to locate the facial and cochlear nerves both electrophysiologically and microscopically, sharp dissection of the facial and cochlear nerves, using forceps, and avoidance of heat and mechanical injury not only to the nerves, but also to the internal auditory artery and the brain stem.[59,60] Based on the senior author's experience in the interventions of nearly 2,500 CPA tumors and 1,500 VSs, the following essential steps of RSSOC approach for optimal outcome are enumerated:

1. General inhalation anesthesia without using paralyzing drugs after induction.
2. Operative position: Lateral, all pressure points padded, the contralateral arm beyond the tabletop, supported on a sling/extension table rest.
3. The head is flexed enough to allow two fingers between the chin and sternum and slightly flexed laterally to the contralateral side. The head is positioned neutral and not rotated. The table is rotated away, to facilitate of reach the IAM and ipsilaterally sideways while dissecting toward brain stem.
4. Four-channel FN monitoring in all and BERA monitoring in patients with good preoperative hearing is routinely carried out.
5. Craniotomy to expose the transverse and sigmoid sinus junction. The authors do not recommend "extended"

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retrosigmoid approach, exposing the sigmoid sinus and retracting the dura with a stay suture. Not only it is redundant, but it also increases the risk of sinus injury and thrombosis. The authors do not utilize image guidance or AI to plan the craniotomy.

6. Foramen magnum is opened in giant tumors, in the presence of significant hydrocephalus, redo surgery, and in the presence of large cystic tumor. It facilitates dural opening below the foramen magnum and releasing CSF and avoids the herniation of cerebellum through the dural opening in large and giant tumors.
7. Ventricular tapping is rarely necessary.
8. The dural opening is slightly curvilinear, convex medially, starting at the transverse–sigmoid sinus junction down to the lower end of craniotomy. There are no lateral cuts, making it easy for good primary closure of the dura at the end of surgery.
9. The first step is to release the CSF from the cerebello-medullary cistern to have a laxed brain. All attempts (diuretics, hyperventilation, or ventricular tap if needed) must be made to have a lax cerebellum before one proceeds to the tumor. Retracting a full/bulging/tense cerebellum is the recipe for disaster.
10. Intradurally, the posterior petrous dura is coagulated with bipolar forceps to reduce the major blood supply to the tumor, mainly by the ascending pharyngeal branches.
11. The glistening arachnoid over the posterior surface of the tumor is peeled off medially to expose the bare tumor. In case of any doubt about the tumor arachnoid plane, it is advisable to err to peel the outer layer of the tumor along with the arachnoid.
12. Tumor decompression is then carried by tumor holding forceps, suction, enucleator, and CUSA, leaving a thick (less than 5 mm) capsule of tumor.
13. The IAC is then drilled after baring the bone of the dura by sharp incision. It is important to remove all patties/cottonoids from the operative field before one starts drilling. Initially a burr and then a diamond drill are used as one reaches near the last layer of bone. It is critical to perform drilling under continuous and copious irrigation to avoid cranial nerve injury due to heat. Wide drilling is done to have 180-degree exposure of the canal so that safe dissection of intracanalicular tumor can be done. Laterally the drilling is usually 5 to 6 mm. Limited lateral drilling is important in hearing-preservation surgery. The lateral part of the tumor beyond the drilled IAC can be removed under endoscope assistance. The intracanalicular tumor is decompressed with dissector-stimulator and low power CUSA.
14. The 7th and 8th cranial nerves are identified in the IAC and then at the medial brain stem end. The landmarks for the 7th and 8th complex at the brain stem is usually 2 to 3 mm superior to the root entry zone of the 9th cranial nerve and in the same plane, just anterior to the flocculus.
15. Lifting of the inferomedial part of the tumor capsule superolaterally along the tumor arachnoid plane from the root exit zone of the 7th cranial nerve under constant nerve monitoring is the safest way of functional preservation. Leaving a thin sliver of tumor capsule on the nerve in large and giant tumors results in best functional outcome. Tracing the 7th and 8th cranial nerves from medial end till the IAM and identifying the nerves in the IAC and tracing them till IAM and leaving the attachment of the tumor capsule to the cranial nerves just medial to IAM till the end provides the best

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chance of good functional preservation and total excision, especially in small and medium size tumors.

16. Leaving the normal structures, the lower cranial nerves, and the 5th cranial nerve covered by arachnoid is the best protection against injury.
17. Although arterial bleeding needs to be controlled by low strength bipolar, the venous bleeding, troublesome on the brain stem end, is best controlled by hemostatic agent and pressure of wet patties.
18. There is no shame in backing off if there is any problem during surgery and come back for a second sitting or send the patient to a more experienced colleague or, if appropriate, resort to radiosurgery.
19. Once the tumor is excised, the operative field is copiously irrigated and a bloodless field is confirmed. The drilled IAC is filled with small pieces of fat and glue. The primary watertight dural closure is reinforced with a thin layer of fat, earlier harvested from the patient's thigh. Large mastoid air cells are filled with fat and glue and sealed with bone wax. A thin layer of fat is used to cover the drilled mastoid area and is sealed with glue.
20. The craniotomy bone is fixed with mini titanium plates (usually two) and the wound is closed in layers without a drain and mastoid dressing is applied.

Following these steps can result in both normal facial function in all sizes of tumors and hearing preservation in high percentage of cases in Koos 1 to 3 tumors and some cases of large and giant VS. Wanibuchi et al[61] and Samii et al[18] in their series could achieve 93% anatomical facial preservation. They also reported that the most critical point of dissection of the FN is the region of entry of the internal acoustic meatus. Superineurial dissection is advised if the tumor cannot be dissected from the 7th and 8th cranial nerves easily.[62] Minimal bipolar coagulation near the nerve and at lower currents with a sharp forceps is essential to minimize electric or thermal injury to the neural structures.[43] Anatomically, it is possible to discern the superior vestibular fibers traveling over the more superior aspect of the tumor, and every attempt should be made to save the fibers in the pursuit to preserve hearing, which also helps protect the 7th cranial nerve.[3] The senior author reported use of sodium fluorescein dye to effectively distinguish the facial and cochlear nerves from the tumor because of their differential enhancement, thus facilitating total excision of the tumor and ensuring preservation of both facial and cochlear nerves.[63]

Over a period of time, the thrust has changed from an attempt of total excision at any cost to preservation of function. This has resulted in significant improvement of facial function. VS being a benign tumor, a small sleeve of tumor left attached to the FN in an attempt to have a better facial function is better and more acceptable to the patient. Often this small residue doesn't need any further treatment. In the event of its growth, it can be safely reoperated or treated by radiosurgery.[64] Total resection may not be always possible in cystic VS; hence, subtotal resection can be targeted.[65]

Complications of Vestibular Schwannoma Surgery

The complications after VS excision can be divided into neurological, vascular, and nonneurological complications[18,43,66–69] (**Table 31.6**). CSF leak, disequilibrium, tinnitus, facial numbness, and chronic headache after VS excision surgery are common complications even after a successful excision.[43] The reported rates of CSF leakage following surgery for VS range widely from 8.1 to 30%.[66,67] CSF rhinorrhea was the most common complication in the series published by Misra et al.[1] CSF can leak in the form of rhinorrhea, otorrhea, or through the incision. Fat graft in

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Table 31.6 Common complications after vestibular schwannoma excision surgery[18,42,66–69]

Neurological complications
Hearing loss
Facial weakness
Disequilibrium
Bothersome tinnitus
Facial numbness
Disturbed taste sensation
Blepharospasm
Hemifacial spasms
Facial pain
Tongue numbness
Delayed hydrocephalus
Vascular complications
Sinus thrombosis
AICA damage causing hearing loss
SCA damage
PICA damage
Vertebral artery damage
Distant cerebral vasospasm
Nonneurological complications
CSF leak
Chronic headaches
Scar pain

Abbreviations: AICA, anterior inferior cerebellar artery; CSF, cerebrospinal fluid; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery.

the drilled IAC and reinforcing of primary dural closure with fat graft sutured over the suture line have significantly reduced the incidence of postoperative CSF leak in authors' practice.

Vascular complications of CPA surgery can be divided into venous and arterial types, and further into hemorrhagic and ischemic injuries. Venous injury is often related to the surgical approach, with the major venous sinuses (transverse, sigmoid, and their junction) being routinely exposed. Furthermore, the potential for long operative time spent mostly under the intense light of the operating microscope renders the sinuses dehydrated and prone to thrombotic events. The best approach of a venous or sinus bleeding is tamponade with hemostatic agent and patties rather than trying to achieve hemostasis by coagulation or suturing an injured sinus. While tamponading a sinus injury, it is important not to push the Gelfoam/Surgicel into the sinus to avoid occluding it. Tumors more than 4 cm in size involve the main ICA trunk or AICA branches, and in a small number of cases AICA vessels are within the tumor. Other vessels involved with large tumors include the superior cerebellar artery, the posterior inferior cerebellar artery, and the vertebral artery.[68] The senior author reported a rare and challenging complication of delayed symptomatic cerebral vasospasm following VS resection with a very high morbidity rate in reported cases. It mentioned that arterial blood in the subarachnoid space can contribute to symptomatic vasospasm after extra-axial posterior fossa tumor removal, very similar to vasospasm following aneurysmal subarachnoid hemorrhage. Hence, a high index of suspicion is required for early diagnosis and prompt management for a favorable outcome.[69]

Incidental Vestibular Schwannoma

With the ease of imaging and a decrease in threshold for imaging the diagnosis of incidental tumors has increased. Hoa and associates systematically reviewed the literature and generated an evidence-based guideline for the care of patients with incidental VS (all level III evidence)[70]:

- Approximately two-thirds of tumors do not grow during a 5-year observation period. Varughese and colleagues demonstrated prospectively that a 5-year cutoff is adequate to distinguish growing from nongrowing tumors.[71]
- Growth within the first year may warrant an early intervention.
- Approximately 50% of patients maintain "good" hearing at 5 years' observation.
- Good hearing is defined as an SDS of 70% or greater.
- Larger initial tumor size may predict future tumor growth.

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- Large tumor size is defined as larger than 1.5 to 2.0 cm.
- Initial hearing loss may predict a greater chance of loss of good hearing over time.
- Poor prognostic signs for hearing preservation include the following: abnormal auditory brain stem response.

Small Vestibular Schwannoma

VSs are classified as small when the tumor is purely intracanalicular, without CPA extension, or when the maximum diameter of the CPA extension is 15 mm or less.[72,73] Currently, the management options for asymptomatic VSs include observation, upfront radiosurgery, and microsurgery. Hearing decline is seen in a significant number of patients who undergo observation over 5 to 10 years.[72,74,75] In their study Kirchmann et al found that the natural history of tumor growth of an intracanalicular VS was 37% over 9.5 years with maximum growth in the first 4.6 years, 23% had extra-meatal extension, and serviceable hearing (AAO-HNS class A or B) was lost in 66% of patients during that period.[74] Johnson et al reported that upfront radiosurgery leads to tumor growth arrest and 94% progression-free survival at 10 years.[76] However, after a large study, Johnson et al reported that the preservation of serviceable hearing (Gardner–Robertson grade 1 or 2) was a challenge as they found 68.4% hearing preservation at 5 years and 51.4% at 10 years.[76] In a systematic review of 2,034 patients with purely intracanalicular tumors and with CPA extension of less than 20-mm diameter who underwent retrosigmoid approach, hearing preservation rates were 47.7% and 35.4%, respectively.[77]

Tips and Technical Nuances

Sasaki et al, in their series of 112 patients with preoperative useful hearing, reported an overall rate of hearing preservation of 52.7 and 64.2% for tumors less than 2 cm.[62] They described the concept of subcapsular/subperineurial dissection to preserve facial and cochlear nerve function. The tumor capsule comprises of vestibular nerve perineurium and nerve fibers; hence, leaving this capsule perineurium avoids direct manipulation of facial and cochlear nerves, thus leading to better preservation of nerve functions.

Large Vestibular Schwannoma

Although the best course of action for a small VS is up for debate, microsurgical excision is typically the best option for treating large VS. Surgical excision of a large VS with the RSSOC approach is consistently found safe as it provides panoramic view of the CPA from the tentorium cerebelli to the foramen magnum, and the retraction of the temporal lobe of the brain is not required. The primary drawback is the restricted exposure of the IAC, which makes it challenging to dissect the tumor laterally.[78] In case of large VS, the chances of hearing preservation decreases if the tumor infiltrates the cochlear nerve, and the preoperative hearing is not serviceable.[2]

A recent systematic review and meta-analysis including nine studies (248 patients) with mean follow-up period of 48 months highlighted the shift toward adoption of the combined subtotal resection followed by stereotactic radiosurgery (SRS) approach for large VS.[79] This surgical philosophy not only offers excellent rates of FN preservation (96.1%), but it also incorporates the possibility of maintaining auditory function (59.9%) while still achieving a tumor control rate comparable to that of total surgical resection (93.9%).[75] This is an important consideration, as it is sometimes overlooked in the pursuit of a total excision in large VS surgery (i.e., the traditional treatment paradigm).[80,81] Because no dissection is attempted between the nerve's plane and the tumor capsule, the planned subtotal resection followed by SRS appears to be associated with the best auditory outcome.[80,81]

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Although there has been a general shift toward planned subtotal resection and radiosurgery in large and giant VS, the senior author has a different approach.[82] The emphasis of functional preservation has been there for many years. However, the aim is total- or near-total excision of the tumor with preservation of function and a low threshold for subtotal excision if there is significant risk of dysfunction, mainly of facial dysfunction, is where the monitoring helps.[64,83–85] Following total excision of Koos grade IV VSs by the senior author, **Fig. 31.1** demonstrates normal facial function (HB grade I) and good hearing and **Fig. 31.2** shows normal facial function (HB grade I) and serviceable hearing after near-total excision of VS. **Fig. 31.3** shows good long-term facial (HB grade II) and auditory (serviceable hearing) function after complete excision of Koos grade IV VS.

Radiation Treatment for Vestibular Schwannoma

The accepted dose for gamma knife radiosurgery (GKRS) is 12 to 14 Gray at 50% isodose.[1] With this dose, the reported long-term control rates are between 93 and 97%. There are occasional reports of even improved hearing after GKRS. The broad indications for GKRS are patients with tumors of 2.5 cm or less in maximum diameter, high medical risk, elderly patients, and/or recurrent or residual tumor showing growth.[1] Pattankar et al[86] in their series proposed a protocol for advising GKRS in VSs which was as follows: (1) in small-to-medium VSs with evidence of radiological progression, options of both GKRS (preferred in age >60 years and those with significant comorbidities) and microsurgery (preferred in age <60 years and without comorbidities)

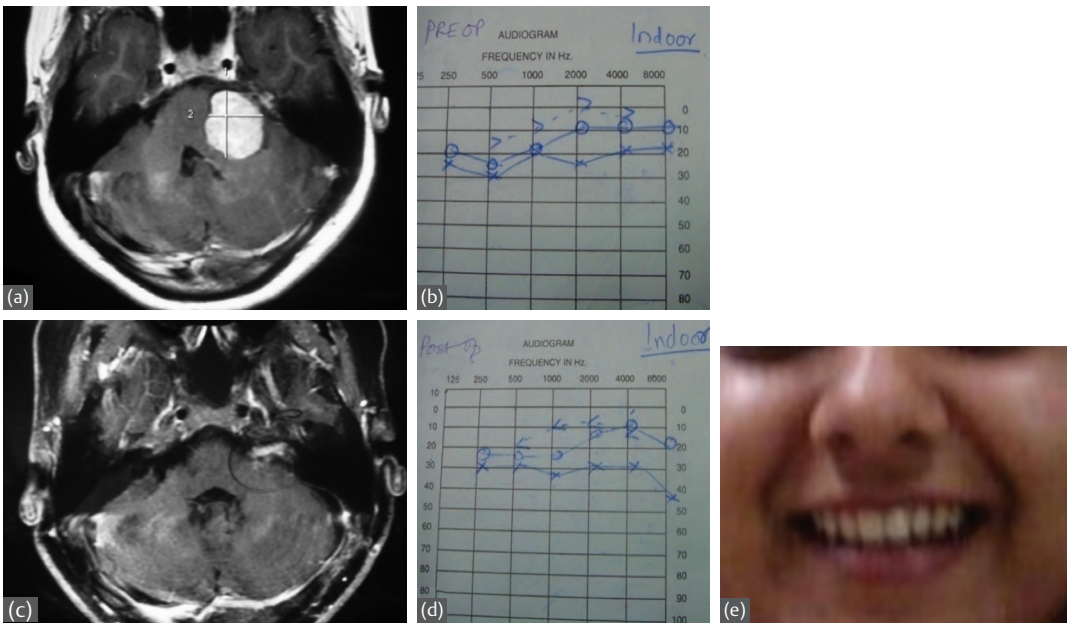

Fig. 31.1 Preoperative magnetic resonance imaging (MRI) of brain showing large (Koos grade IV) left vestibular schwannoma **(a)** and preoperative audiometry showing normal left ear hearing **(b)**. Immediate postoperative MRI of brain shows total excision of the tumor. The enhancement in the internal auditory canal (IAC) (circled) is postoperative changes **(c)**; 7 days postoperative audiometry shows good hearing in left ear **(d)**, and 3-month postoperative clinical image shows normal face (HB grade I) **(e)**.

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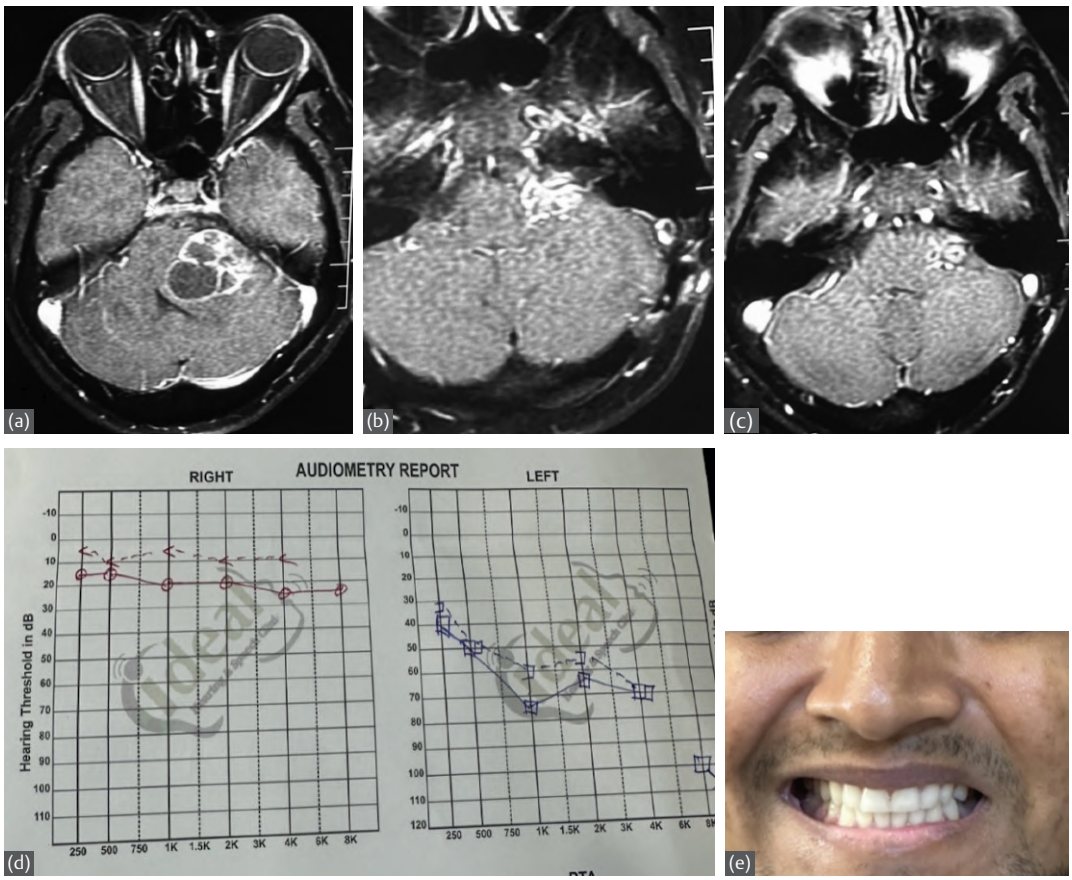

Fig. 31.2 Preoperative magnetic resonance imaging (MRI) of brain showing large (Koos grade IV) solid-cystic left vestibular schwannoma **(a)**. MRI of brain at 4 months postoperatively shows a small(?) residual tumor **(b)** and 9-month postoperative MRI of brain **(c)** shows decrease in the contrast-enhancing lesion suggesting postoperative changes. Postoperative audiometry at 9 months showing serviceable hearing in left ear **(d)** and the clinical image showing normal face (HB grade I) **(e)**.

are given; (2) in large VSs with brain stem compression, option of microsurgery followed by GKRS for residual/recurrent tumor (nerve-centered approach) is preferred; and (3) in NF-2 patients, the same above-mentioned protocols are used based on the size of VSs.[1] Special counseling was done regarding expected GKRS outcomes in NF-2 compared to sporadic VS cases.[86] Long term post-interventional hearing loss (if the pre-treatment hearing function was class 1 or 2 as per Gardener-Robertson modified hearing classification) was overall 54%, with significantly higher rate of hearing loss in surgery (63%) compared to SRS (46%). The hearing outcome was comparable in both the treatment arms for smaller tumors (Koos grade I and II) while for larger tumors (Koos grade III and IV), SRS was superior to surgery.[87] Past long-term studies have reported hearing preservation rates of 63 to 68% at the last follow-up in studies with similar follow-up lengths in SRS.[88,89] However, it remains undocumented whether even longer follow-up might uncover more delayed cases of hearing loss after SRS or even surgery. Future studies should aim to

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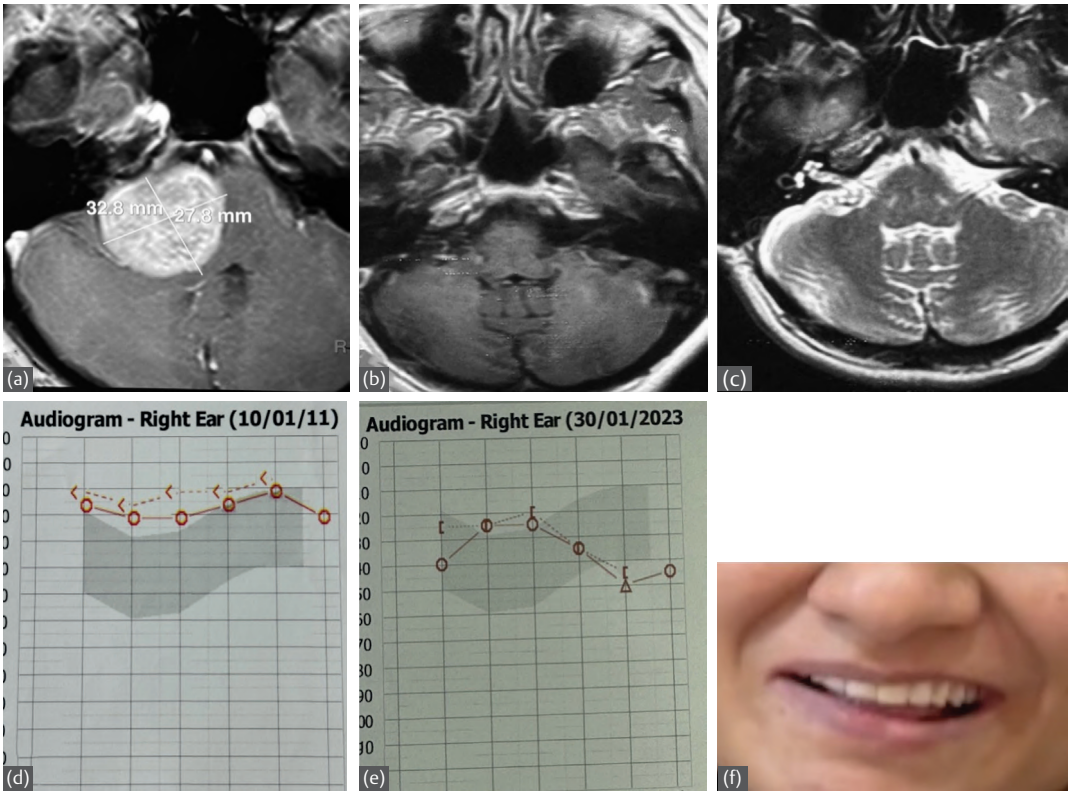

Fig. 31.3 Preoperative magnetic resonance imaging (MRI) of brain showing large (Koos grade IV) right vestibular schwannoma **(a)**. MRI of brain at 12 years postoperatively **(b, c)** shows complete excision of the tumor. Preoperative audiometry showing mild hearing loss **(d).** Audiometry at 12 years postoperatively shows serviceable hearing in right ear **(e)** and postoperative clinical image shows mild facial weakness (HB grade II) **(f)**.

investigate this aspect of long-term functional outcomes. SRS was superior to surgery in facial function preservation, especially in large VS, which is concordant to a prospective comparative study by Myrseth et al.[90] The data showed a direct postinterventional facial paresis of approximately 30% of Koos grade III and Koos grade IV VS tumors, right after surgery.[1] Park et al in their retrospective study of 106 patients with unilateral sporadic VSs who underwent GKRS as an initial treatment, found the tumor control rates were 94.3% at 5 years and 87.7% at 10 years.[91] High radiation dosages would be necessary for large tumors, increasing the possibility of radiation damage to the healthy tissue. Instead, a combination of subtotal tailored microsurgery followed by immediate (within 3 months) or delayed SRS is used to provide long-term control while reducing the risk of cranial nerve damage.[92] **Fig. 31.4** demonstrates good facial preservation (HB grade II) after redo subtotal excision by the senior author of a giant residual VS and GKRS for the small residual tumor. The main distinction between microsurgery and radiosurgery for small Koos grade I and II VSs is how hearing preservation is achieved. Time-based reporting analysis reveals a distinct pattern of gradually declining hearing throughout the 10-year follow-up following radiation therapy, whereas patients who have hearing following microsurgical

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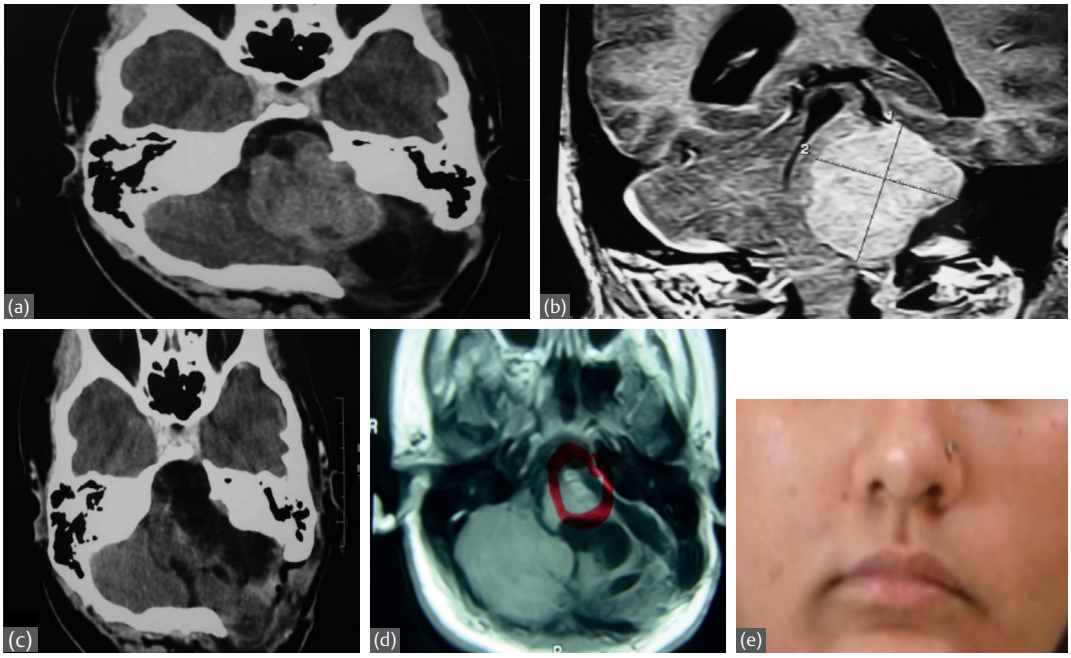

Fig. 31.4 Preoperative computed tomography (CT) of brain **(a)** and magnetic resonance imaging (MRI) of brain **(b)** showing a giant (Koos grade IV) residual left vestibular schwannoma. Immediate postoperative CT of brain shows near-complete excision of the tumor **(c),** and 3-month postoperative MRI of brain shows a small residual tumor to which GKRS was given **(d)**. Clinical image at 3-month follow-up shows mild facial weakness (HB grade II) **(e)**.

excision typically do so.[93] Therefore, if hearing is preserved, young individuals with good hearing may benefit from complete microsurgical removal of the tumor.

Microsurgery Following Radiation

Misra and Churi in their study of 16 patients with an average follow-up of 50 months, who underwent microsurgery following radiation, observed that the tumors found at surgery were firmer, with an avascular core but increased vascularity near the surface, and thickened arachnoid with adhesions to the surrounding structures, hence making total excision difficult and near-total excision was employed in these cases to preserve facial function. Out of 11 who underwent gross-total/near-total resection, 8 patients had grade I/II HB facial function, 4 had grade III, and 3 had grades IV/V. Of the last three, two had the same deficit preoperatively. None of the patients needed any further radiosurgery/microsurgery since the last intervention.[45] Severe fibrous adhesions between the tumor capsule and surrounding neurovascular systems, as well as fibrous and persistent transformation of the tumor tissue, present some unusual surgical challenges in the resection of radiation-failed VSs which may result in inadequate neural structure preservation and, as a result, increase the likelihood of postoperative facial weakness and hearing loss.[43,45,46,94–96] The senior author has reported an unusual case of a malignant transformation in a VS post radiation and an unusual case of cystic recurrence post radiation.[97]

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Conservative Approach—"Wait and Scan" Policy

The hearing may degrade to a nonserviceable level in VS patients kept under observation and surveillance.[97] Additionally, in some "wait and scan" studies, during the observation period, tumor growth in young and middle-aged individuals have recorded progression in the hearing loss.[98] However, these options—SRT and wait and scan—remain undeniably crucial for few very small tumors. The recent trend has been in favor of radiosurgery as the control rates of tumor was better. A recent prospective study demonstrated upfront radiosurgery demonstrated a significantly greater tumor volume reduction at 4 years than a wait-and-scan approach with treatment upon tumor growth. However, there was no change in the hearing preservation rates in both the arms. It is important to note that 56% of the tumors did not show growth in one of the longest follow-ups of 10 years of intracranial tumors.[45,46,93–103] Kirchmann et al[74] demonstrated failure of conservative treatment in only 15%, growth in 37%, and growth into the CPA in 23%. Serviceable hearing and the word recognition score were 34 and 58%, respectively. Hearing was better in patients with 100% SDS at diagnosis than in patients even with a small loss of SDS. It is important to distinguish between intracanalicular tumor and tumors with intracisternal extension. The authors recommend a wait and watch approach for most intracanalicular tumors (Koos grade I) and upfront treatment for the tumors with intracisternal extension (Koos grade II and III tumors). The authors' current practice for Koos grade I to III tumors is shown in **Figs. 31.5** and **31.6.**

Conclusion

VS is a common benign brain tumor. Appropriately and managed at the right time, the patient remains fully functional and can be cured. It is also important to remember that all patients with VS do not require intervention and there are different ways of managing a given patient with VS—observation and surveillance, radiosurgery, and microsurgery. While different microsurgical approaches are recommended for different size and presentation of VS, the retrosigmoid approach is appropriate for all types of VS where microsurgery is indicated. It is better to master one technique, and the authors would recommend RSSOC for microsurgery of VS. Leaving thin sliver of tumor to preserve better function is always better than a compromised function after total excision. Finally, microsurgery is not medicine and quoting the literature for the results has no relevance. Every neurosurgeon should find the paradigm that is best in her/his hands. Auditing one's own results and the outcome of the last 100 cases managed by the neurosurgeon should be the basis of her/his recommendation for the 101st patient!

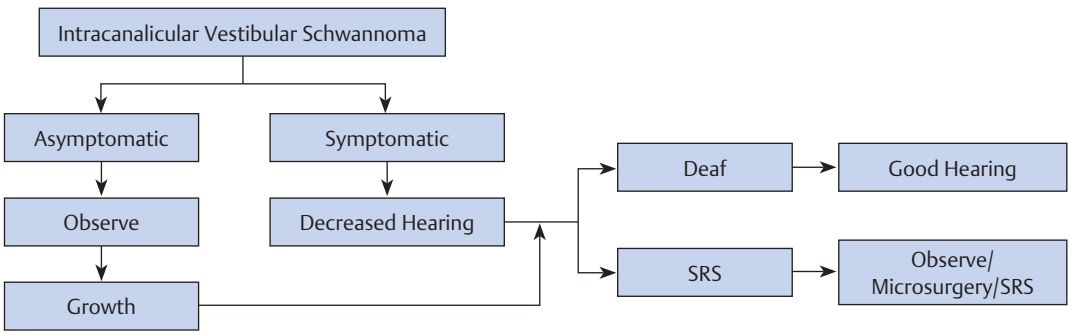

Fig. 31.5 Current practice for intracanalicular vestibular schwannoma (Koos grade I).[1] SRS, stereotactic radiosurgery.

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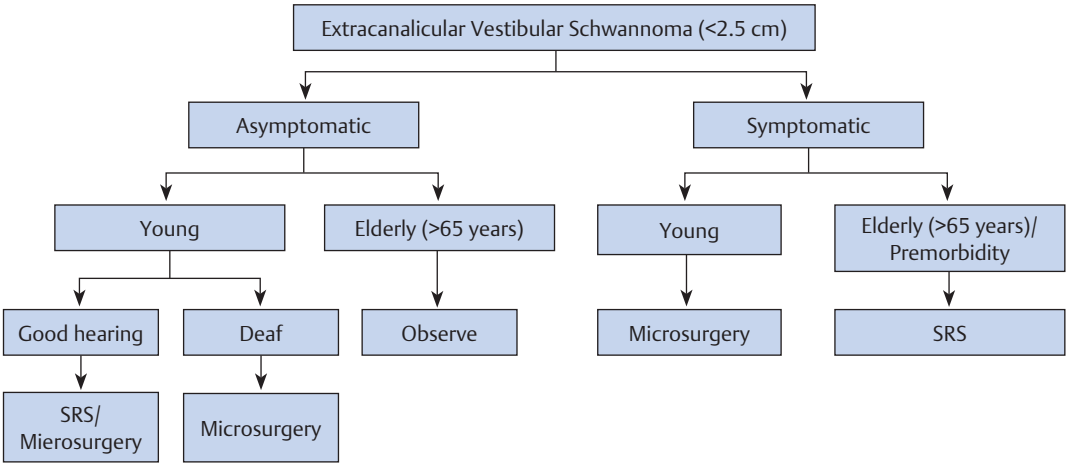

Fig. 31.6 Current practice for vestibular schwannoma with intracisternal extension (Koos grades II and III).[1] SRS, stereotactic radiosurgery.

Preservation of facial function following microsurgery in all sizes of tumors and hearing preservation in Koos grade I and II tumors should be the goal of treatment.

References

1. Misra BK, Purandare HR, Ved RS, Bagdia AA, Mare PB. Current treatment strategy in the management of vestibular schwannoma. Neurol India 2009;57(3):257–263
2. Rajput MSA, Ahmad AN, Arain AA, et al. Preservation of hearing and facial nerve function with the microsurgical excision of large vestibular schwannomas: experience with the retrosigmoid approach. Cureus 2018;10(12):e3684
3. Kunal V, Brian N, Matthew C, Colin D, Michael L. J. Vestibular schwannomas. In: Youssef Samy, ed. Contemporary Skull Base Surgery. Springer Nature Switzerland AG; 2022:551–567
4. Mahaley MS Jr, Mettlin C, Natarajan N, Laws ER Jr, Peace BB. Analysis of patterns of care of brain tumor patients in the United States: a study of the Brain Tumor Section of the AANS and the CNS and the Commission on Cancer of the ACS. Clin Neurosurg 1990;36:347–352
5. Wong RX, Low HYT, Tan DYH. Local experience with radiosurgery for vestibular schwannomas and recommendations for management. Singapore Med J 2018;59(11):590–596
6. Smouha EE, Yoo M, Mohr K, Davis RP. Conservative management of acoustic neuroma: a meta-analysis and proposed treatment algorithm. Laryngoscope 2005;115(3):450–454
7. Foley RW, Maweni RM, Jaafar H, McConn Walsh R, Javadpour M, Rawluk D. The impact of primary treatment strategy on the quality of life in patients with vestibular schwannoma. World Neurosurg 2017;102:111–116
8. Lees KA, Tombers NM, Link MJ, et al. Natural history of sporadic vestibular schwannoma: a volumetric study of tumor growth. Otolaryngol Head Neck Surg 2018;159(3):535–542
9. Tos M, Charabi S, Thomsen J. Clinical experience with vestibular schwannomas: epidemiology, symptomatology, diagnosis, and surgical results. Eur Arch Otorhinolaryngol 1998;255(1):1–6
10. van de Langenberg R, de Bondt BJ, Nelemans PJ, Dohmen AJ, Baumert BG, Stokroos RJ. Predictors of volumetric growth and auditory deterioration in vestibular schwannomas followed in a wait and scan policy. Otol Neurotol 2011;32(2):338–344
11. Caces F, Braccini F. Evaluation de la chirurgie stapédienne pour otospongiose par le score de bénéfice de Glasgow compare aux critères de l'AAO-HNS: résultats sur 129 cas. [Comparative study using AAO-HNS guidelines for conductive hearing loss and Glasgow Benefit Plot to evaluate results of stapes surgery for otosclerosis: results of 129 cases] Rev Laryngol Otol Rhinol (Bord) 2007;128(1-2):47–53
12. Marinelli JP, Lohse CM, Grossardt BR, Lane JI, Carlson ML. Rising incidence of sporadic vestibular schwannoma: true biological shift

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versus simply greater detection. Otol Neurotol 2020;41(6):813–847
13. Plotkin SR, Merker VL, Muzikansky A, Barker FG II, Slattery W III. Natural history of vestibular schwannoma growth and hearing decline in newly diagnosed neurofibromatosis type 2 patients. Otol Neurotol 2014;35(1):e50–e56
14. Reznitsky M, Petersen MMBS, West N, Stangerup SE, Cayé-Thomasen P. The natural history of vestibular schwannoma growth—prospective 40-year data from an unselected national cohort. Neuro-oncol 2021;23(5):827–836
15. Sterkers JM, Morrison GA, Sterkers O, El-Dine MM. Preservation of facial, cochlear, and other nerve functions in acoustic neuroma treatment. Otolaryngol Head Neck Surg 1994;110(2):146–155
16. Hitselberger WE, House WF. Classification of acoustic neuromas. Arch Otolaryngol 1966;84(3): 245–246
17. Koos WT, Day JD, Matula C, Levy DI. Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas. J Neurosurg 1998;88(3):506–512
18. Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and how to avoid them. Neurosurgery 1997;40(1):11–21, discussion 21–23
19. Committee on Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma). American Academy of Otolaryngology-Head and Neck Surgery Foundation, INC. Otolaryngol Head Neck Surg 1995;113(3):179–180
20. Gardner G, Robertson JH. Hearing preservation in unilateral acoustic neuroma surgery. Ann Otol Rhinol Laryngol 1988;97(1):55–66
21. Vellutini EA, Beer-Furlan A, Brock RS, Gomes MQ, Stamm A, Cruz OL. The extracisternal approach in vestibular schwannoma surgery and facial nerve preservation. Arq Neuropsiquiatr 2014; 72(12):925–930
22. Sweeney AD, Carlson ML, Ehtesham M, Thompson RC, Haynes DS. Surgical approaches for vestibular schwannoma. Curr Otorhinolaryngol Rep 2014; 2:256–264
23. Cass Nathan D, Gubbels Samuel P. Middle fossa approach for hearing preservation. In: Youssef Samy, ed. Contemporary Skull Base Surgery. Springer Nature Switzerland AG; 2022:437–449
24. Budohoski KP, Rennert RC, Gordon SA, et al. Factors associated with hearing outcomes after a middle fossa approach in 131 consecutive patients with vestibular schwannomas. J Neurosurg 2022; 139(2):432–441
25. Samii M, Gerganov V, Samii A. Improved preservation of hearing and facial nerve function in vestibular schwannoma surgery via the retrosigmoid approach in a series of 200 patients. J Neurosurg 2006;105(4):527–535
26. Brackmann DE, Cullen RD, Fisher LM. Facial nerve function after translabyrinthine vestibular schwannoma surgery. Otolaryngol Head Neck Surg 2007;136(5):773–777
27. Briggs RJS, Luxford WM, Atkins JS Jr, Hitselberger WE. Translabyrinthine removal of large acoustic neuromas. Neurosurgery 1994; 34(5):785–790, discussion 790–791
28. Bruzzo M, Broder L, Chays A, Magnan J. Nos résultats actuels de la chirurgie du neurinome de l'acoustique.. (Ref. 28 "Bruzzo, Broder, Chays, Magnan, 2000. [Our current results with acoustic neurinoma surgery]. Ann Otolaryngol Chir Cervicofac 2000;117(2): 110–117
29. Colletti V, Fiorino FG. Retrosigmoid-transmeatal en bloc removal of small to medium-sized acoustic neuromas. Otolaryngol Head Neck Surg 1999; 120(1):122–128
30. House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg 1985;93(2): 146–147
31. Sughrue ME, Yang I, Rutkowski MJ, Aranda D, Parsa AT. Preservation of facial nerve function after resection of vestibular schwannoma. Br J Neurosurg 2010;24(6):666–671
32. Axon PR, Ramsden RT. Facial nerve injury caused by vestibular schwannoma compression: severity and adaptation to maintain normal clinical facial function. Am J Otol 1999;20(6):763–769
33. Falcioni M, Fois P, Taibah A, Sanna M. Facial nerve function after vestibular schwannoma surgery. J Neurosurg 2011;115(4):820–826
34. Seol HJ, Kim CH, Park CK, et al. Optimal extent of resection in vestibular schwannoma surgery: relationship to recurrence and facial nerve preservation. Neurol Med Chir (Tokyo) 2006;46(4):176–180, discussion 180–181
35. Sobieski C, Killeen DE, Barnett SL, et al. Facial nerve outcomes after vestibular schwannoma microsurgical resection in neurofibromatosis type 2. Otolaryngol Head Neck Surg 2021;164(4): 850–858
36. Isaacson B, Kileny PR, El-Kashlan H, Gadre AK. Intraoperative monitoring and facial nerve

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outcomes after vestibular schwannoma resection. Otol Neurotol 2003;24(5):812–817
37. Oh T, Nagasawa DT, Fong BM, et al. Intraoperative neuromonitoring techniques in the surgical management of acoustic neuromas. Neurosurg Focus 2012;33(3):E6
38. Churi ON, Gupta S, Misra BK. Correlation of preoperative cranial nerve diffusion tensor tractography with intraoperative findings in surgery of cerebellopontine angle tumors. World Neurosurg 2019;127:e509–e516
39. Savardekar AR, Patra DP, Thakur JD, et al. Preoperative diffusion tensor imaging-fiber tracking for facial nerve identification in vestibular schwannoma: a systematic review on its evolution and current status with a pooled data analysis of surgical concordance rates. Neurosurg Focus 2018;44(3):E5
40. Chen DQ, Quan J, Guha A, Tymianski M, Mikulis D, Hodaie M. Three-dimensional in vivo modeling of vestibular schwannomas and surrounding cranial nerves with diffusion imaging tractography. [published correction appears in Neurosurgery. 2011 Jun;68(6): E1780] Neurosurgery 2011; 68(4):1077–1083
41. Olson JJ, Kalkanis SN, Ryken TC. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the treatment of adults with vestibular schwannomas: executive summary. Neurosurgery 2018;82(2):129–134
42. Farid AM, Elkholy AR. Preservation of facial nerve functions during vestibular schwannoma surgery: outcome analysis. Egypt J Neurosurg 2019;34(1):25
43. Nonaka Y, Fukushima T, Watanabe K, et al. Contemporary surgical management of vestibular schwannomas: analysis of complications and lessons learned over the past decade. Neurosurgery 2013;72(2, Suppl Operative):ons103–ons115, discussion ons115
44. Ramina R, Jung GS, Constanzo F, da Silva EB, Coelho Neto M. Intracanalicular vestibular schwannomas: facial and hearing outcomes according to the location of the tumor in relation to the nerves of the internal auditory canal. J Neurosurg 2023;139(4):984–991
45. Misra BK, Churi ON. Microsurgery of vestibular schwannoma post-radiosurgery. Neurol India 2019;67(5):1274–1278
46. Hosmann A, Hari S, Misra BK. Cystic recurrence of vestibular schwannoma post-radiosurgery: an institutional experience. Acta Neurochir (Wien) 2023;165(12):4149–4156
47. Jacob JT, Carlson ML, Driscoll CL, Link MJ. Volumetric analysis of tumor control following subtotal and near-total resection of vestibular schwannoma. Laryngoscope 2016;126(8):1877–1882
48. Simon MV. Neurophysiologic intraoperative monitoring of the vestibulocochlear nerve. J Clin Neurophysiol 2011;28(6):566–581
49. Roberson J, Senne A, Brackmann D, Hitselberger WE, Saunders J. Direct cochlear nerve action potentials as an aid to hearing preservation in middle fossa acoustic neuroma resection. Am J Otol 1996;17(4):653–657
50. Arts HA, Telian SA, El-Kashlan H, Thompson BG. Hearing preservation and facial nerve outcomes in vestibular schwannoma surgery: results using the middle cranial fossa approach. Otol Neurotol 2006;27(2):234–241
51. Yamakami I, Yoshinori H, Saeki N, Wada M, Oka N. Hearing preservation and intraoperative auditory brainstem response and cochlear nerve compound action potential monitoring in the removal of small acoustic neurinoma via the retrosigmoid approach. J Neurol Neurosurg Psychiatry 2009;80(2):218–227
52. Ahmed S, Arts HA, El-Kashlan H, Basura GJ, Thompson BG, Telian SA. Immediate and long-term hearing outcomes with the middle cranial fossa approach for vestibular schwannoma resection. Otol Neurotol 2018;39(1):92–98
53. Dowling EM, Patel NS, Lohse CM, et al. Durability of hearing preservation following microsurgical resection of vestibular schwannoma. Otol Neurotol 2019;40(10):1363–1372
54. Starnoni D, Giammattei L, Cossu G, et al. Surgical management for large vestibular schwannomas: a systematic review, meta-analysis, and consensus statement on behalf of the EANS skull base section. Acta Neurochir (Wien) 2020;162(11):2595–2617
55. Scheller C, Wienke A, Tatagiba M, et al. Stability of hearing preservation and regeneration capacity of the cochlear nerve following vestibular schwannoma surgery via a retrosigmoid approach. J Neurosurg 2016;125(5):1277–1282
56. Sepehrnia A, Borghei-Razavi H. Vestibular schwannoma between 1 and 3 cm: importance of the tumor size in surgical and functional outcome. Clin Neurol Neurosurg 2015;129:21–26
57. Wang AC, Chinn SB, Than KD, et al. Durability of hearing preservation after microsurgical treatment of vestibular schwannoma using the middle cranial fossa approach. J Neurosurg 2013;119(1):131–138
58. Zhu W, Chen H, Jia H, et al. Long-term hearing preservation outcomes for small vestibular

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schwannomas: retrosigmoid removal versus observation. Otol Neurotol 2018;39(2):e158–e165
59. Fukushima T, Nonaka Y, Day JD, et al, eds. Exercise 8: Combined Neurotology-Neurosurgery Skull Base Approaches. In: Fukushima Manual of Skull Base Dissection. 3rd ed. Raleigh, NC: AF-Neurovideo Inc.; 2010:210–249
60. Shrivastava A, Nair S. Commentary: "Save the nerve": technical nuances for hearing preservation and restoration in vestibular schwannoma surgery: 2-dimensional operative video. Oper Neurosurg (Hagerstown) 2021;21(4):E330–E331
61. Wanibuchi M, Fukushima T, Friedman AH, et al. Hearing preservation surgery for vestibular schwannomas via the retrosigmoid transmeatal approach: surgical tips. Neurosurg Rev 2014; 37(3):431–444, discussion 444
62. Sasaki T, Shono T, Hashiguchi K, Yoshida F, Suzuki SO. Histological considerations of the cleavage plane for preservation of facial and cochlear nerve functions in vestibular schwannoma surgery. J Neurosurg 2009;110(4):648–655
63. Misra BK, Jha AK. Potential utility of sodium fluorescein can distinguish tumor from cranial nerves in vestibular schwannoma surgery. Neurol India 2021;69(4):1087–1088
64. Misra BK. Surgery for giant acoustic neuroma: total excision at what cost. World Neurosurg 2012;77(5-6):625–626
65. Shrivastava A, Nair A, Nair S. Vestibular schwannoma: half a decade odyssey from challenges to functional preservation. Neurol India 2020;68(2):262–263
66. Magliulo G, Sepe C, Varacalli S, Fusconi M. Cerebrospinal fluid leak management following cerebellopontine angle surgery. J Otolaryngol 1998;27(5):258–262
67. Arlt F, Trantakis C, Krupp W, et al. Cerebrospinal fluid leak after microsurgical surgery in vestibular schwannomas via retrosigmoidal craniotomy. Neurol Res 2011;33(9):947–952
68. Sampath P, Rini D, Long DM. Microanatomical variations in the cerebellopontine angle associated with vestibular schwannomas (acoustic neuromas): a retrospective study of 1006 consecutive cases. J Neurosurg 2000;92(1):70–78
69. Pasricha P, Khandhar AV, Misra BK. Delayed symptomatic cerebral vasospasm following vestibular schwannoma resection: illustrative case. J Neurosurg Case Lessons 2024;7(9):CASE2374
70. Hoa M, Drazin D, Hanna G, Schwartz MS, Lekovic GP. The approach to the patient with incidentally diagnosed vestibular schwannoma. Neurosurg Focus 2012;33(3):E2
71. Varughese JK, Breivik CN, Wentzel-Larsen T, Lund-Johansen M. Growth of untreated vestibular schwannoma: a prospective study. J Neurosurg 2012;116(4):706–712
72. Pennings RJ, Morris DP, Clarke L, Allen S, Walling S, Bance ML. Natural history of hearing deterioration in intracanalicular vestibular schwannoma. Neurosurgery 2011;68(1):68–77
73. Yamakami I, Ito S, Higuchi Y. Retrosigmoid removal of small acoustic neuroma: curative tumor removal with preservation of function. J Neurosurg 2014; 121(3):554–563
74. Kirchmann M, Karnov K, Hansen S, Dethloff T, Stangerup SE, Caye-Thomasen P. Ten-year follow-up on tumor growth and hearing in patients observed with an intracanalicular vestibular schwannoma. Neurosurgery 2017;80(1):49–56
75. Sughrue ME, Kane AJ, Kaur R, et al. A prospective study of hearing preservation in untreated vestibular schwannomas. J Neurosurg 2011; 114(2):381–385
76. Johnson S, Kano H, Faramand A, et al. Long term results of primary radiosurgery for vestibular schwannomas. J Neurooncol 2019;145(2):247–255
77. Kim YH, Kim DG, Han JH, et al. Hearing outcomes after stereotactic radiosurgery for unilateral intracanalicular vestibular schwannomas: implication of transient volume expansion. Int J Radiat Oncol Biol Phys 2013;85(1):61–67
78. Nelson RF, Hansen MR, Gantz BJ. Hearing preservation surgery for vestibular schwannomas. Curr Otorhinolaryngol Rep 2014;2(4):235–241
79. Starnoni D, Daniel RT, Tuleasca C, George M, Levivier M, Messerer M. Systematic review and meta-analysis of the technique of subtotal resection and stereotactic radiosurgery for large vestibular schwannomas: a "nerve-centered" approach. Neurosurg Focus 2018;44(3):E4
80. Daniel RT, Tuleasca C, George M, et al. Preserving normal facial nerve function and improving hearing outcome in large vestibular schwannomas with a combined approach: planned subtotal resection followed by gamma knife radiosurgery. Acta Neurochir (Wien) 2017;159(7):1197–1211
81. Iwai Y, Ishibashi K, Watanabe Y, Uemura G, Yamanaka K. Functional preservation after planned partial resection followed by gamma knife radiosurgery for large vestibular schwannomas. World Neurosurg 2015;84(2):292–300

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82. Misra BK. Management strategy in acoustic neuroma. In: Emilio GI, Tran Ba Huy P, eds: 5th International Conference on Vestibular Schwannoma and Other CPA Lesions. Medimond. Srl., Italy. 2007:47–52
83. Misra BK. Management of acoustic neuroma. In: Kalangu K, ed. Essentials in Neurosurgery. WFNS; 2010:313–327
84. Pattankar S, Churi O, Misra BK. Validation of the Penn Acoustic Neuroma Quality of Life (PANQOL) scale for Hindi-speaking patients recently diagnosed with vestibular schwannoma. Neurol India 2022;70(3):978–982
85. Pattankar S, Churi O, Misra BK. Quality of life in patients of unilateral vestibular schwannoma treated with microsurgery: a South-Asian tertiary care hospital experience. J Clin Neurosci 2021;89: 264–270
86. Pattankar S, Pasricha P, Misra BK. SRS for vestibular schwannomas—current status. Neurol India 2023; 71(Suppl):S115–S122
87. Tatagiba M, Wang SS, Rizk A, et al. A comparative study of microsurgery and gamma knife radiosurgery in vestibular schwannoma evaluating tumor control and functional outcome. Neurooncol Adv 2023;5(1):vdad146
88. Hasegawa T, Fujitani S, Katsumata S, Kida Y, Yoshimoto M, Koike J. Stereotactic radiosurgery for vestibular schwannomas: analysis of 317 patients followed more than 5 years. Neurosurgery 2005;57(2):257–265, discussion 257–265
89. Pollock BE, Driscoll CL, Foote RL, et al. Patient outcomes after vestibular schwannoma management: a prospective comparison of microsurgical resection and stereotactic radiosurgery. Neurosurgery 2006;59(1):77–85, discussion 77–85
90. Myrseth E, Møller P, Pedersen PH, Lund-Johansen M. Vestibular schwannoma: surgery or gamma knife radiosurgery? A prospective, nonrandomized study. Neurosurgery 2009;64(4): 654–661, discussion 661–663
91. Park HR, Jeong SS, Kim JH, et al. Long-term outcome of unilateral acoustic neuromas with or without hearing loss: over 10 years and beyond after gamma knife radiosurgery. J Korean Med Sci 2023;38(40):e332
92. Mathiesen T, Förander P, Pettersson D. Schwannomas. In: Kirollos R, Helmy A, Thomson S, Hutchinson P, eds. Oxford Textbook of Neurological Surgery. Oxford University Press; 2019
93. Coughlin AR, Willman TJ, Gubbels SP. Systematic review of hearing preservation after radiotherapy for vestibular schwannoma. Otol Neurotol 2018; 39(3):273–283
94. Pollock BE. Management of vestibular schwannomas that enlarge after stereotactic radiosurgery: treatment recommendations based on a 15 year experience. Neurosurgery 2006;58(2):241–248, discussion 241–248
95. Slattery WH III. Microsurgery after radiosurgery or radiotherapy for vestibular schwannomas. Otolaryngol Clin North Am 2009;42(4):707–715
96. Iwai Y, Yamanaka K, Yamagata K, Yasui T. Surgery after radiosurgery for acoustic neuromas: surgical strategy and histological findings. Neurosurgery 2007;60(2, Suppl 1):ONS75–ONS82, discussion ONS82
97. Stangerup SE, Caye-Thomasen P, Tos M, Thomsen J. Change in hearing during "wait and scan" management of patients with vestibular schwannoma. J Laryngol Rhinol Otol 2008;122(7): 673–681
98. Meyer TA, Canty PA, Wilkinson EP, Hansen MR, Rubinstein JT, Gantz BJ. Small acoustic neuromas: surgical outcomes versus observation or radiation. Otol Neurotol 2006;27(3):380–392
99. Hosmann A, Kamdar V, Misra BK. Malignant transformation of vestibular schwannoma following radiosurgery—a case report and review of the literature. Acta Neurochir (Wien) 2024;166(1):52
100. Régis J, Carron R, Park MC, et al. Wait-and-see strategy compared with proactive gamma knife surgery in patients with intracanalicular vestibular schwannomas. J Neurosurg 2010; 113(Suppl):105–111
101. Kaltoft M, Stangerup SE, Caye-Thomasen P. Facial nerve function after vestibular schwannoma surgery following failed conservative management. Neurosurgery 2012;70(2):278–282, discussion 282
102. Bakkouri WE, Kania RE, Guichard JP, Lot G, Herman P, Huy PT. Conservative management of 386 cases of unilateral vestibular schwannoma: tumor growth and consequences for treatment. J Neurosurg 2009;110(4):662–669
103. Charabi S, Thomsen J, Mantoni M, et al. Acoustic neuroma (vestibular schwannoma): growth and surgical and nonsurgical consequences of the wait-and-see policy. Otolaryngol Head Neck Surg 1995;113(1):5–14

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